UNITED STATES OF AMERICA

+ + + +

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

+ + + +

ARTHRITIS ADVISORY COMMITTEE

+ + + +

PUBLIC HEARING
NSAID COX-2 SAFETY ISSUES

+ + + +

TUESDAY,
MARCH 24, 1998

The hearing was held in Salons A, B, and C at the Gaithersburg Hilton, 620 Perry Parkway, Gaithersburg, Maryland at 8:00 a.m., DR. MICHELLE PETRI, Committee Chairman, presiding.

MEMBERS PRESENT:

MICHELLE PETRI, M.D., M.P.H., Chairman
STEVEN B. ABRAMSON, M.D.
KENNETH D. BRANDT, M.D.
LEIGH F. CALLAHAN, Ph.D.
FELIX FERNANDEZ-MADRID, M.D., Ph.D.
NIGEL E. HARRIS, M.D.
ILDY M. KATONA, M.D., CAPT MC, USN
MATTHEW H. LIANG, M.D., M.P.H.
LEONA M. MALONE
KEVIN R. McCONNELL, M.D.
LARRY W. MORELAND, M.D.
FRANK PUCINO, JR., Pharm.D.
LEE S. SIMON, M.D.
DAVID E. YOCUM, M.D.

KATHLEEN REEDY
Executive Secretary

ALSO PRESENT:

Gastrointestinal Advisory Committee:

LOREN LAINE, M.D.

Food and Drug Administration:

MICHAEL WEINTRAUB, M.D.
JOHN E. HYDE, M.D., Ph.D.
JAMES WITTER, M.D., Ph.D.

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

(8:06 a.m.)

CALL TO ORDER, INTRODUCTIONS

CHAIRMAN PETRI: I want to welcome all of you to the Arthritis Advisory Committee meeting. Our agenda today includes safety issues, gastrointestinal tolerability, renal, bone, and reproductive toxicity related to NSAID COX-2 and other agents.

My name is Michelle Petri. I am from the Johns Hopkins University School of Medicine. And I'd like to have our Committee members and FDA representatives introduce themselves. And we'll start with Dr. Weintraub.

DR. WEINTRAUB: Michael Weintraub, the Director of ODE V and Acting Director of this division.

DR. HYDE: John Hyde, Acting Deputy for Analgesic and Anti-Inflammatory Drugs.

DR. WITTER: Jim Witter, Medical Officer.

MEMBER FERNANDEZ-MADRID: Felix Fernandez-Madrid, Wayne State University.

MEMBER CALLAHAN: Leigh Callahan, University of North Carolina, Chapel Hill.

MEMBER BRANDT: Ken Brandt, Indiana University School of Medicine.

MEMBER SIMON: Lee Simon, Beth Israel Deaconess Medical Center, Boston.

MEMBER LIANG: Matt Liang, Brigham and Women's Hospital in Boston.

EXECUTIVE DIRECTOR REEDY: Kathleen Reedy, Food and Drug Administration.

MEMBER ABRAMSON: Steve Abramson, Hospital for Joint Diseases, NYU.

MEMBER YOCUM: Dave Yocum, University of Arizona, Tucson.

MEMBER KATONA: Ildy Katona, the Uniformed Services University, a pediatric rheumatology and a pediatric person on the panel.

MEMBER HARRIS: Nigel Harris, Morehouse School of Medicine.

MEMBER MALONE: Leona Malone, consumer representative.

MEMBER MORELAND: Larry Moreland, University of Alabama at Birmingham.

MEMBER PUCINO: Frank Pucino, National Institutes of Health.

MEMBER McCONNELL: Kevin McConnell, Charlottesville, Virginia. I'm an oncologist.

DR. LAINE: Loren Laine, USC School of Medicine, Los Angeles, gastroenterologist.

CHAIRMAN PETRI: Thank you.

I'm now going to turn the microphone over to Kathleen Reedy.

MEETING STATEMENT

EXECUTIVE DIRECTOR REEDY: "This is a conflict of interest statement for the Arthritis Advisory Committee meeting on March 24th, 1998. The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

"In accordance with 18 United States Code 208, general matters waivers have been granted to all Committee participants who have interests in companies or organizations which could be affected by the Committee's discussion of NSAID COX-2 agents. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30, Parklawn Building.

"In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement. And their exclusion will be noted for the record.

"With respect to all other participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they may wish to comment upon."

CHAIRMAN PETRI: Thank you.

Dr. Weintraub will now give us a welcome and introduction.

WELCOME AND INTRODUCTION

DR. WEINTRAUB: Good morning. In addition to the members of the Arthritis Advisory Committee, we have other members of different advisory committees here this morning, the GI, and we have experts from nephrology. The question is why.

And the answer really -- we could have had many more experts. We could have hade experts from the pulmonary group or the cardiovascular group. But the question we are facing today, the COX-2, safety or toxicity of COX-2 inhibitors, which may have a differential effect predominantly on the GI tract but also on kidneys and bone and even possibly on the reproductive system, the CNS, et cetera, although in a sense the whole body. And that's why we have so many different people here, to give us a feeling of ability to integrate all of these different body systems.

We also know that when a drug like Coxuidin comes along, it may lose some toxicity. It may gain other kinds of toxicity. And they may be subtle and difficult to understand, to determine.

In addition, everyone realizes, I think, that the toxicity of nonsteroidal anti-inflammatory agents, both their morbidity and their mortality, really have a negative effect on the public health, predominantly, although not exclusively, in the elderly. And that's a very important aspect of our work: to protect the public health.

Now, fortunately, we have experts today, such as a gastroenterologist, Dr. Laine, who will help us get started on the discussion of the GI aspects of current NSAIDs and of COX-2 agents. Dr. Laine will not only start the discussion, but also I think, I am hoping, that he will be able to act as a resource for us all day today.

Now, the GI side effects may occupy a lot of our time and a lot of our questions, but they won't take all of either our time or our questions. And we have a nephrologist, Dr. McConnell, who will again present and discuss the known renal effects of NSAIDs and of COX-2 agents.

We'll be able to discuss both of these

topics with each expert. As I mentioned, I hope that they will be able to be technical backstops for us. And we can question them throughout the day.

Now, personally I really don't approve of class labeling. I believe we should be looking for small differences between drugs. So each one of you should say, "Why is he working at the FDA? And why did he start out at the FDA and is still very closely associated with OTC monographs, which are the ultimate in class labelings?"

Well, sometimes we have to put aside our personal opinions and say, "Look, it's important to have some kinds of class labeling"; for example, in the GI warning section for nonsteroidal anti-inflammatory drugs.

If we didn't have the class labeling, we would have to deal with small differences coming from studies done in different populations under different conditions with different doses of drugs at different times. And we would have to be explaining to the American physicians and to the population as well what the difference between 2.6 and 4.1 was.

So we have decided and we have I hope provided all of you with copies of the NSAID class labeling, what we called a GI template, which

represents our attempt to describe the warnings of a general nonsteroidal anti-inflammatory drug and how we view its warnings in a reasonable way.

Since people will be trying to generate evidence to change the GI warning or the clinical trial section portion of the label, we're going to ask you what kinds of evidence, what types of trials will suffice to alter the label. We're not going to ask you to do our job, but we're going to ask you to concentrate on the type of evidence that you would find persuasive in changing the label.

Now, the last thing I'd like to say this morning is that although we like to -- "we" being the people from the FDA, like to -- listen actively and to think about what people in the open public hearing and our experts, people from the audience say and think and, most of all, what you, our advisers, say and think. I've asked the FDA people to jump in and be more active, not just to listen but to participate in the discussions.

Sometimes we do do this, and sometimes I don't think we do enough. But I'm hoping that today we will be active and participatory. And I hope this won't disturb the chemistry of the Committee. And I hope it will be you as Committee members would be able

to continue to perform your important task; that is, to be our advisers and counselors.

Thanks, Michelle.

CHAIRMAN PETRI: Thank you.

We're now going to have an open public hearing. There are two registered speakers during the open public hearing. The first one is Steven Geis, Executive Director of Clinical Research at G. D. Searle and Company.

For those speakers who have slides, I will ask some of our Committee members to move over to the side chairs so that we'll be able to see them.

Dr. Geis?

DR. GEIS: Thank you, Dr. Petri.

OPEN PUBLIC HEARING

1. G. D. SEARLE & COMPANY

DR. GEIS: Good morning, ladies and gentlemen. And thank you for the opportunity to share some of our ideas. The focus of today's discussion is on a new class of agent-specific COX-2 inhibitors.

And, as all of you know, prostaglandins, which are mediators in both health and disease, are produced by the enzyme cyclooxygenase. And this enzyme exists in two forms: COX-1 and COX-2.

COX-1, the constitutive form, produces

prostaglandins that maintain homeostasis in vital organ systems, such as the GI tract, the kidney, and platelets. COX-2, the inducible form, is up-regulated under certain circumstances and produces prostaglandins that pay a role in pain and inflammation.

NSAIDs are nonspecific or nonselective inhibitors of cyclooxygenase. They're efficacious in treating the signs and symptoms of rheumatoid arthritis and osteoarthritis due to inhibition of COX-2, but they also produce mechanism-based side effects due to their inhibition of COX-1.

And these side effects are not trivial. There are approximately 8,000 deaths in the United States alone due to NSAID use, and there are tens of thousands of hospitalizations per year due to NSAID side effects. And these are predominantly GI side effects.

Specific COX-2 inhibitors are being designed to block COX-2 without affecting COX-1. They're expected to be as efficacious as NSAIDs in treating the signs and symptoms of rheumatoid arthritis and osteoarthritis but without the side effects of NSAIDs.

Should this new class of agents satisfy

our expectations, they could dramatically alter arthritis care and could dramatically alter the quality of life of patients with arthritis. But if we are to advance arthritis care with this new class of compound, we must establish criteria that must be met before a compound is classified as, promoted as, or used as a specific COX-2 inhibitor.

I'd like to share with you some of our recommendations of what these criteria should be. A thorough development program should be carried out that shows clear evidence of COX-2 selectivity across the entire spectrum of preclinical and clinical studies.

The compound should demonstrate COX-2 selectivity in *in vitro* enzyme assays and in well-established animal models of COX-1 and COX-2 activity. But evidence of selectivity in these models is really not completely sufficient.

Animal models might not be clinically relevant. A compound that is shown to be 1,000-fold selective for COX-2 in an enzyme assay is only meaningful when it's supported by clinical evidence.

Therefore, we believe that an extensive clinical program should efficacy and especially GI safety should be conducted for any compound purported

to be a specific COX-2 inhibitor.

First of all, replicate clinical trials should show the analgesic and anti-inflammatory properties of the compound. The trials should be conducted according to FDA guidelines and should demonstrate efficacy for treating the signs and symptoms of osteoarthritis and rheumatoid arthritis and should demonstrate the compound alleviates pain.

GI safety that is superior to NSAIDs but similar to placebo should also be demonstrated by clinical studies. Well-controlled endoscopy trials should be conducted for comparing the incidence of gastroduodenal ulcers of the alleged specific COX-2 inhibitor versus NSAIDs.

These trials should include three or more NSAIDs and should be well-controlled. The duration should be at least three months. And the definition of ulcers should be prospectively defined.

Full therapeutic doses of the NSAIDs and the specific COX-2 inhibitors should be used in these studies. The trials should be replicated. And in some of the studies, serial monthly endoscopies should be performed.

The study results should routinely show a statistical and clinically significant reduction in

the incidence of gastroduodenal ulcers with the specific COX-2 inhibitor compared to NSAIDs. Furthermore, the results should demonstrate that there is no difference in the incidence of ulceration between the specific COX-2 inhibitor and placebo.

Now, many investigators believe that endoscopic ulcers are surrogates for clinically significant upper GI events, such as bleeding, perforation, and gastric upload obstruction. Although we support this concept for NSAIDs, since specific COX-2 inhibitors are a new class of compound, we recommend that the development program for any potential specific COX-2 inhibitor should include assessments of clinically significant upper GI events.

As was the case in the mucosa trial that we conducted several years ago and published, an external committee of GI experts should be established. The Committee should prospectively define the criteria that must be met for an event to be considered a clinically significant upper GI event. The Committee should then review all potential cases of upper GI events in a blinded fashion and then determine which events were, in fact, clinically significant and which were not.

A true specific COX-2 inhibitor should

demonstrate an incidence of clinically significant upper GI events that is clearly lower than that of NSAIDs.

Also, as with any new compound, the safety profile of an agent of a purported specific COX-2 inhibitor should be described by analyzing all reported adverse events throughout the clinical program. In addition, specific studies should be conducted to look at the effects of these compounds on the kidney and on platelets.

Currently there are a number of specific COX-2 inhibitors undergoing development throughout the industry. There will be differences among these specific compounds. There will be differences in chemical structure. There will be differences in the *in vitro* selectivity, the potency, and the pharmacology.

These differences, in turn, can translate into differences in efficacy and safety. Therefore, we believe that the merits of each new specific COX-2 inhibitor should be determined uniquely for that specific inhibitor by the extent of the clinical data, the quality of the data, and the clinical relevance of that data.

Thank you for your attention.

CHAIRMAN PETRI: Let me ask if any of the Committee members have a question or comment.

(No response.)

CHAIRMAN PETRI: Then we'll move on to the next registered speaker. Robert Palmer is the Director of Rheumatology in SmithKline Beecham Pharmaceuticals.

Dr. Palmer?

2. SmithKLINE BEECHAM PHARMACEUTICALS

DR. PALMER: Good morning. Members of the Advisory Panel, ladies and gentlemen, thank you for the opportunity to make a few comments that perhaps reflect a slightly contrary point of view.

My name is Dr. Robert Palmer. And I'm Director of Rheumatology at SmithKline Beecham. I'm also a gastroenterologist. So I have a particular interest in certain complications of NSAID therapy.

In your folder, you have a packet of the slides I will be presenting that are displayed two to a page. And you can use that to follow and make notes if you wish.

Behind that is an expanded presentation, which was originally the initial presentation before I cut it down, that has some additional information and references.

Today I would like to make two main points. First, a high degree of COX-2 activity is not necessarily predictive of safety, nor is it necessary as some dual or balanced inhibitors of cyclooxygenase have excellent safety. Second, categorization of NSAIDs should not be based on isoenzyme selectivity. It should be based on relevant clinical events.

Simply put, the old hypothesis considered that COX-1 was a constitutive enzyme with a primary role in providing prostaglandins that participate in homeostasis and protection. COX-2 was considered to be an inducible enzyme responsible for prostaglandin synthesis and inflammation.

An inhibitor of COX-2 should completely suppress inflammation without interfering with physiological functions. We now know that this construct is oversimplified.

The actual situation is that these two isoenzymes have overlapping functions. On the one hand, COX-1, which can be up-regulated in response to injury, clearly participates in the inflammatory response.

On the other hand, COX-2 clearly as important physiological functions in addition to participating in inflammatory. In the GI tract, COX-2

plays a role in tissue repair, also epithelial integrity. And it could be it also contributes renal vascular homeostasis.

Recent data also suggest it might play a role in ovarian function and fertility, cartilage repair, and vascular prostaglandin formation. Therefore, its inhibition may lead to traditional NSAID side effects and/or may disclose a new spectrum of side effects.

This leads to a revised hypothesis. For anti-inflammatory efficacy, it may be advantageous to inhibit both COX-1 and COX-2. However, to preserve normal physiological function, it may be desirable to retain some residual activity of both isoenzymes.

But obtaining a satisfactory anti-inflammatory response with highly selective inhibitors may require such complete inhibition of one isoenzyme that it may be unable to perform its physiological role and toxicity results. In fact, it may be undesirable to have a highly selective enzyme. In other words, dual COX inhibition may be preferable.

These concepts are illustrated in this schematic. A highly selective COX-1 inhibitor may not produce unwanted effects until COX-1 is almost completely inhibited. Conversely, there may be

important COX-2 functions that are unaffected until there is fairly complete inhibition of COX-2.

Are there any examples of this? Yes. Complete inhibition of COX-1 with aspirin abolishes thromboxane synthesis of platelets and leaves them completely unable to aggregate. This, as you know, may be a major contributor to GI bleeding.

However, the addition of as little as two and a half percent of normal platelets to aspirin-treated platelets provides adequate thromboxane to fully restore their ability to function. Thus, preservation of even small amounts of COX-1 functionality may be adequate to prevent this particular form of toxicity.

Similarly, a variable amount of COX-2 inhibition may be tolerated depending on the situation. A modest amount of activity may be sufficient to permit normal ulcer healing and normal renal function; whereas, complete inhibition of COX-2 may impair ulcer healing, as has been demonstrated in animals.

Can COX-2 inhibition contribute to NSAID toxicity? We'll turn first to the kidney. You will recall that COX-2 is normally expressed in rat, dog, and human kidneys. And COX-2 in the macula densa of

animals is up-regulated by volume depletion. Further, COX-2 inhibition affects renal function in animals.

This slide shows the effect of a highly selective COX-2 inhibitor at doses of 3, 10, and 30 micromoles per kilogram on renal plasma flow in conscious, chronically restrained, volume-depleted female dogs.

The top line, in blue, is the placebo vehicle alone. The white line is a highly selective COX-2 inhibitor. And the orange line is a dual COX inhibitor.

Renal plasma flow with a selective COX-2 inhibitor was significantly lower than baseline and significantly lower than with a vehicle. There was no significant change with a dual inhibitor at any dose and no significant difference from the vehicle. Essentially similar effects were observed with glomerular filtration rate, urine flow, sodium excretion, and urinary prostaglandin B2 excretion.

We conclude that COX-2 inhibition can influence renal homeostasis. The fact that the dual COX inhibitor did not affect function may be because it did not completely inhibit either enzyme or, more likely, it may have to do with the absence of active drug in the glomerular filtrate in the tubule.

We turn now to the question of whether COX-2 inhibition prevents NSAID-induced GI toxicity. In the GI tract, we are concerned with PUBs. This unfortunate term lumps together uncomplicated ulcers, which are less important because 40 percent of them heal spontaneously while the NSAID is continued and complications due to peptic ulcer or other lesions. The latter should be the focus of our concern because they carry a high rate of morbidity and mortality.

As Dr. Geis mentioned, there are eight to ten thousand deaths a year from complications of NSAID administration. And reducing this by 80 percent could make a major difference.

With respect to GI damage, we know that COX inhibition is not the whole story. NSAID ulcers occur in COX-1 knockout mice, who have no COX-1 to inhibit. Further, prostaglandin replacement does not completely prevent NSAID ulcers.

As noted, many NSAID ulcers heal spontaneously without any sequelae, even when NSAIDs are continued without anti-secretory treatment. However, it seems reasonable, though not proven, that impaired healing might lead to chronicity; more penetration; and, therefore, more complications of bleeding and perforation. That is why it is important

that COX-2 inhibition has been shown to impair ulcer healing in animals.

Clinically possible effects of a drug on ulcer healing will not be demonstrated in short-term endoscopic studies that examine the incidence of new ulcers. To demonstrate those effects would require special healing studies or long-term clinical outcome studies of three months or more, in which ulcers of any etiology are occurring and may not be healing adequately.

This potential effect on healing has to be taken seriously because Dr. Stenson noted in his recent editorial on this subject of COX-2 inhibition, "inflammatory and wound healing form a seamless continuum; drugs that inhibit inflammation may also retard healing."

So how much COX-2 activity is desirable? We would want to inhibit both isoenzymes for good anti-inflammatory efficacy, but complete COX-2 inhibition may not ensure safety and complete absence of COX-1 inhibition is not necessary for safety. These points can be inferred from clinical data.

When looking at uncommon events, it may be useful to express the rates in terms of events per 100 patient-years, as is done in many epidemiologic

studies.

With Drug A, a dual COX inhibitor, total PUBs occur at a rate of about .4 per 100 patient-years. This is an order of magnitude less than seen with more COX-1 selective NSAIDs, such as those used in the control group in the MUCOSA study, shown on the right. 5.4. And it is not dissimilar from the background rate of 0.7.

But only 25 percent of those PUBs were complicated ulcers. The rate of complicated ulcer, about .1 per 100 patient-years, is much less than that seen with the other NSAIDs. Note that this compound is not a highly selective COX-2 inhibitor.

In summary, we would suggest that highly selective NSAIDs are still NSAIDs. Both COX isoenzymes participate in inflammation. And inhibition of either or both may contribute to anti-inflammatory activity.

Both COX isoenzymes have physiological roles. And function can be maintained when some activity is preserved. Toxicity may result from complete and irreversible inhibition of either isoenzyme, giving either traditional or unexpected toxicity.

Finally, there clearly are additional

factors that may sensitize patients to the effects of enzyme inhibition. So the toxicity occurs when it would not under normal circumstances. For example, in the kidney in patients who are buying depleted or inhibitors and then GI tract in patients who are elderly, have had previous ulcers, et cetera.

Therefore, high COX-2 activity is not necessarily predictive of more safety. And some dual inhibitors have excellent safety. In the last analysis, safety or toxicity may be a function both of exposure of the isoenzyme to the drug, whether it's in the gastric mucosa or in the tubular urine, and to the extent of isoenzyme inhibition as well as other factors.

We suggest that categorization of NSAIDs should not be based on isoenzyme selectivity but should be based on relevant clinical events measured in appropriate populations.

For GI complications, relevant clinical events mean complicated or serious lesions. For renal events, it means looking for outcomes in an at-risk population using a positive control.

Thank you.

CHAIRMAN PETRI: Thank you.

Did any of the Committee members have a

comment or question for Dr. Palmer?

(No response.)

CHAIRMAN PETRI: Are there other unregistered participants for the open public hearing? If so, would you please go to the microphone?

(No response.)

CHAIRMAN PETRI: Seeing none, we'll move on to our scheduled speakers. The first is Dr. Loren Laine.

Dr. Laine?

DR. LAINE: Thank you very much. The audience gets to see my best side.

In any event, I've been asked to give a general overview on the gastrointestinal effects of NSAIDs and really to do a kind of a baseline basic, hopefully not too simple job discussing what effects the NSAIDs that are available now cause in the GI tract. And I'm going to be talking only about clinical human studies and only about things that are actually in the literature, as opposed to kind of proprietary things.

So first I want to show a bunch of pictures just to show you what the lesions that NSAIDs cause look like, both endoscopically and histologically. And the lights are kind of high here,

but this is what hemorrhagic gastritis, a term that we don't like, but hemorrhages due to NSAIDs look like in the stomach, kind of like batiki. I like blood under Saran Wrap, if you will.

And if you were to biopsy this, this is what you would see: lots and lots of red blood cells directly beneath the epithelium in the top portion, the most superficial portion, of the mucosa.

Just as an aside, people use the term "gastritis" a lot, but, as we'll see, there really isn't a true gastritis present. This is a totally normal mucosa here as compared to a true gastritis. Where you see lots and lots of inflammatory cells here in the mucosa, this is the classic gastritis we're talking about histologically when we talk about *H. Pylori*-associated gastritis. So there's a marked difference between the two.

This is just a high-powered view. It only notes red blood cells beneath the epithelium. Now, these are erosions. This is what erosive, quote, "gastritis" or "gastropathy" looks like through the endoscope.

You see these white-based basically flat lesions with a halo of erythema about them. And if you per chance decided to biopsy one of them and look

at them, this is a mucosal specimen here.

And you can see there's a divot, a little break, in the mucosa, but it's remaining confined to the superficial-most portion of the gastric mucosa. It does not break through. This is the muscularis mucosae separating the mucosa from the next lower layer of the submucosa.

And just to show you for those who like histology, there are some abnormalities in the histology of people who have erosions. You can sometimes even see a pseudo membrane, kind of like pseudo membranous colitis. You can see corkscrewing very reactive cells, but this is kind of a typical picture of an NSAID-associated lesion.

Now, erosions and ulcers are a really important point to distinguish. The difference between an erosion and an ulcer is clearly a histologic or a pathologic one. And an erosion by definition is a break in the mucosa which remains confined in the mucosa. An ulcer by definition is when that break goes down into the submucosa or deeper.

And, as you know, the intestinal tract has four layers; right: mucosa, submucosa, muscular layer. In the basement is a serosa. And this is

clinically important for the following two reasons. You really don't have any significant bleeding when you only have an erosion.

There are no major blood vessels up here to cause major bleeding. In order to get major bleeding, this break has to go down into the submucosa or deeper in order to get blood vessels like this to get really big-time bleeding.

In addition, clearly you can't get a perforation until this lesion goes all the way through all the layers of the GI tract. So it's an important distinction clinically. And although endoscopists always say, "Oh, this is an erosion" or "This is an ulcer," the bottom line is you really can't tell for sure in all cases. And that's one of the concerns that we have when we do endoscopic studies. And we'll talk more about that in a minute.

This is what an ulcer looks like endoscopically. But, frankly, if we just saw this ulcer in an asymptomatic patient, we wouldn't care about it. The thing we really care about is preventing this: blood spurting across the room, as you see here in this patient with a major bleeding ulcer. So this is the biggest concern, obviously, as the previous speakers have mentioned.

As I mentioned, there are concerns when you are doing these GI trials because endoscopic diagnosis can be difficult, despite the fact that people always just say, "That's an ulcer," "That's an erosion."

What size to use? People have traditionally used three millimeters. Some say, "Oh, we shouldn't use three. We should use five." People say we should use larger ulcers because larger ulcers take a longer time to heal. There is evidence that the larger the ulcer, the greater the chance of rebleeding if the ulcer is bled.

And I think what people always say, although I don't know that there are great data about this, if it's bigger, it's more likely to be an ulcer, less likely to be an erosion because it's probably deeper as well.

And, as I mentioned, people typically define an ulcer as depth, perceptible depth. But, again, that can be in the eye of the beholder. Although I don't think we're there yet, -- we were having a meeting yesterday discussing this -- it would be interesting in the future to have objective documentation. And hopefully soon the technology will be available to actually have mechanisms to actually

document that there is depth to this ulcer, that it's not merely just what some endoscopist says in a study in some center.

Let's talk about how often these NSAIDs cause injury. It's quite dramatic. There's no doubt that NSAIDs are the most important exogenous cause of gastric injury, GI tract injury in the world, certainly in the United States.

If everybody in this room took just a couple of aspirin tablets and we endoscoped ourselves an hour later, all of us would have those hemorrhages I showed you earlier.

Now let's say we just continued taking the aspirin for one day, 24 hours, and we rescoped ourselves at the end of 24 hours. All of us would have those erosions that I talked about earlier.

Now, again, this is perhaps from a topical injury and we need to separate the topical injury from the systemic and probably more important injury that is caused from, again, systemic effects of these NSAIDs.

But, in any event, everybody gets a GI injury when they take aspirin, as an example of an NSAID. Clearly not everybody who is taking an NSAID regularly has a lesion if you were to endoscope them,

but if you took a large group of people who are regularly using NSAIDs off the street and convinced them all to undergo endoscopy, you'd find erosions in about 50 percent and ulcers in perhaps 15 to 30 percent. So it's a very common problem, at least endoscopically.

Just as an aside, I wanted to show you two of the studies that are the longest-term follow-up looking at the cumulative incidence of endoscopic ulcers. Remember we're talking about endoscopic, not clinically significant, ulcers at this point.

These are the two studies where there is 6 to 12-month follow-up with repeated endoscopies over 6 to 12 months. And I should mention most of these patients, as you can see, did not have an ulcer at pre-entry, when they were screened.

What you can see is over a 12-month period in this study, there was a slow increase, up to close to 30 percent of patients having an ulcer cumulative incidence.

And it's interesting. We'll talk about complications flattening out later perhaps. In this study as well, it's interesting to see that the ulcers tended to flatten out around three to six months, both of these studies, I should say.

So we can say that NSAIDs increase the risk of ulcers and more often they increase the risk of gastric and duodenal ulcers, but much more important clinically is that they increase, as you all know, the risk of ulcer complications. And that relative risk can be generally in the ball park of two to five-fold, although you can find numbers all over the place. It is interesting that they increase the risk of both gastric and duodenal ulcers, said to be relatively similar in number.

A more important question is: How often do these complications occur? We saw that ulcers are incredibly common, but we know that NSAID-associated GI complications are much less common.

I would echo Dr. Palmer's comments. I really have a hard time with this FDA PUB two to four percent number because I think that's kind of silly, frankly. The P and the B are okay, but the U is really kind of meaningless.

As we heard, 30 percent of people have ulcers. So if you're endoscoping everybody, lots of people have ulcers. And if you're endoscoping nobody, you won't find any ulcers. So that two to four percent I think for PUB is kind of silly. And I don't really like the U in the PUB idea.

So with that in mind, really, what can we say about the incidence of the development of NSAID-associated GI complications in the literature? And you can find numbers all over the place. Let me just show you two studies that kind of give you a low end and a high end of numbers.

Gabriel in the meta analysis that people always quote found a .1 percent one year prevalence of GI events, as she called them. And Dr. Silverstein, here in the first row, in the MUCOSA trial reported perhaps one of the somewhat higher numbers but probably one of the best studies, clearly, at really giving us real numbers, about a three-quarters of one percent incidence of obstruction, perforation, or bleeding at six months. The problem is there are marked variations in these studies depending on other risk factors. So let's just look at these two studies.

If you look at Gabriel, the numbers range from as low as .03 per year to as high as .32 per year. And in Dr. Silverstein's and colleagues' study, if all four risk factors which they defined were present, there was a nine percent rate of GI complications. So we know that the rate of GI complications is low, .1 to 1 or 1 and a half percent

per year perhaps, but it's quite variable depending on the risk factors of the population you're studying.

So it's really important to try to decide which ulcers will remain innocuous and which ulcers are going to be causing serious problems. And we aren't able to do that well, but I think this is a major issue for us since most ulcers will never cause a patient any problems.

So what are some of the risk factors for ulcer complications with NSAID use? This is very controversial. Some people's lists would be very different than mine. But these are things that I think are reasonable, and I've listed them in perhaps some sort of decreasing order, although we can all argue about that.

I think everybody agrees that a history of ulcers or previous GI complications is the most important risk factor. And we should always ask our patients about that, if nothing else.

Concomitant anticoagulation use, Cumidin therapy, steroid use, these increase the risk, it seems. Older patients seem to have a higher risk of complications and patients with other major illnesses, especially, let's say, heart disease, as defined in the MUCOSA trial, and people using high-dose or

multiple NSAIDs. These are all apparent risk factors for ulcer complications to occur with NSAID use.

Something else that I always find interesting is a suggestion that has been shown in multiple trials. This is from the Gabriel meta analysis. And these are odds ratios here on the x-axis.

What this and other studies have shown is that it seems that the risk of bleeding or having other GI complications is most important and highest in the first week or month of therapy. And this has been shown in more than one study, which I always find rather interesting.

There are a number of explanations which we can talk about later, but, in any event, there are a number of studies to suggest that when you start NSAIDs, you may actually have a higher risk of developing complications, perhaps finding clinically silent ulcers, which become clinically manifest when you start the NSAID.

Saying that, there's at least one experimental study by Kurata and Abbey looking at a large MI prophylaxis study using a little higher-dose aspirin. They showed kind of a linear increase over time. It may be flattening out there, but this is

about a three to four-year follow-up here on the hospitalization.

And you can see that using hospitalization for ulcer disease as your indication of GI complication, there's kind of a linear increase. And it wasn't a slope, as many of the others show here. There may be differences in these different studies. But at least some studies may suggest a somewhat linear increase over time.

Now, something that's very important and not really related to COX-2 per se is the large and increasing use of aspirin as a means of vascular prophylaxis. So lots and lots of our patients are taking doses of aspirin at 325 and 81 milligrams. In Europe, even 30 milligrams has been shown to be effective for vascular prophylaxis.

The first question is: Does low-dose aspirin still cause a risk in terms of GI complications? And, as this study and others have shown, yes, it does seem to still show an increase in complications. It seems as you give more aspirin, the odds ratio increases. But please note that all the 95 percent confidence intervals here overlap quite markedly. In any event, this shows us an even 81 milligrams, which a lot of patients are using now, for

prophylaxis still has a risk of GI complications.

Now, some have suggested: Well, what if we give less, 30, 10, milligrams? Will we still get the vascular prophylactic effect but avoid the GI toxicity?

Well, in a study from Mark Feldman's group in Dallas, they actually looked at the effect of low-dose aspirin on prostaglandin production. And let's just look at these two figures on the left.

What they showed is that -- the y-axis, I should mention, is the percent of baseline prostaglandins when measured at three months. What they showed is the decrease in prostaglandins with 10 milligrams was at least as much as that seen with 81 and 325 milligrams, suggesting that any dose of aspirin may at least have the potential for causing GI complications.

One last thing that always comes up: What about enteric-coated aspirin? Intuitively, we would think that enteric-coated aspirin would cause just the same number of problems.

We know that initially in the first week, there are less endoscopic lesions seen, but since the salicylate levels will be the same and we know that it seems to be systemic effect, rather than topical

effect, that is important, we would assume that enteric-coated aspirin would have the same risk.

And in this study from the *Lancet*, you can see here the red line is the relative risk and these are the confidence intervals, that all of these forms of aspirin at low dose have similar and significant elevations in terms of development of upper GI bleeding. So any dose in any form seems to be a potential problem.

Now we have to realize that we always think about the upper GI tract in terms of NSAIDs, but NSAIDs can cause problems throughout the GI tract. NSAIDs can cause ulcers, strictures, and diaphragms in the small intestine.

I won't belabor this, but just to show you a picture to wake people up, here's a picture from an article showing these strictures, these diaphragms in the small intestine at an autopsy series.

NSAIDs also can cause problems in the colon. They can cause a colitis, ulcers, and strictures. And I think of great interest is the fact that they can have an adverse effect on preexisting disease. For instance, if a patient has inflammatory bowel disease, there's some evidence that NSAIDs will increase the chance of exacerbation.

Now, we shouldn't say only bad things about NSAIDs because in the GI tract, NSAIDs, as you know, have been shown to be beneficial in terms of the prevention or reduction in risk of colonic neoplasia.

And since we're talking about COX-2 in a little while, experimental models suggest that the reason that NSAIDs cause inflammatory bowel disease to relapse but also the reason that they are protective against colorectal neoplasia is due to the COX-2 inhibition, perhaps rather than general or COX-1 inhibition.

So, getting to the meat of the matter perhaps, we want to try to decrease NSAID-induced GI injury. So what do we do? Obviously you try to use a non-NSAID analgesic if you can. You want to use as low a dose as you can in cotherapies. And then what we are here to discuss I guess later today is the development of less injurious NSAIDs.

Just briefly I wanted to mention a little bit about some of the trials because there are a number of large trials of cotherapy preventing NSAID-associated ulcers. And I think this is important as a baseline as you go further today to discuss development of new guidelines for development of clinical trials.

As I think people know, although H2 receptor antagonists have been the most commonly used drugs by physicians in patients taking NSAIDs, there is clear evidence that these are not really helpful at standard dose in preventing gastric and duodenal ulcers.

There is one study out now that showed that double-dose Frimodidine, double-dose H2 receptor antagonist, was effective at decreasing the incidence over a six-month period of development of both gastric and duodenal ulcers. So perhaps high-dose H2 blockers may be effective.

Probably the most information has been generated in studies of misoprostol. This is one study which was among the best that clearly showed that endoscopically, over a three-month period with repeated endoscopies, there was a significant decrease in the cumulative incidence of endoscopically observed duodenal and gastric ulcers, as compared to placebo.

Now, as I've mentioned, all of these are endoscopic studies. And I think we need to keep coming back to this. These are endoscopic studies. And the question is: Can we extrapolate these endoscopic endpoints to the clinically important endpoints that you've heard about, like bleeding,

perforation, et cetera?

And also, as you have heard, there is really very, very little information to allow us to know if that's possible or not. Probably the most ambitious study is the one you have already heard about, the so-called MUCOSA trial. And this is a compilation, a table of the results. Let's just focus on this third line here.

As you can see, if you look at perforation, obstruction, or bleeding, you can see that there is approximately a 50 percent reduction as compared to placebo with the use of the agent misoprostol.

And this was significant. It was only significant if you lumped all the complications together. If you looked at the separate compilation, let's say, bleeding, it did not achieve statistical significance.

Certainly we can quibble about the study as much as we want, but I think this is an extremely ambitious and important study. And what it does suggest perhaps is that these endoscopic endpoints perhaps at least can be extrapolated, at least qualitatively, to these clinical events.

Now just to be very topical, in the last

week in the *New England Journal*, there were two articles of some very large studies from Europe by Chris Hawkey and colleagues. And I'll just share with you these, just the idea that proton pump inhibitors, as compared to H2 blockers, appear to be more effective at preventing the development of ulcers in the stomach and the duodenum and that proton pump inhibitors, as compared to misoprostol, were approximately the same, perhaps a little better in duodenal ulcer disease, as you can see here. So we have a new player as well in terms of prevention of NSAID-associated endoscopic ulcers.

Now, I think it's important when we look at these studies, we really need to look carefully -- and also we need to define studies -- at the patient population that is studied because when you look at these studies, you can have very different outcomes, depending on which route you enrolled.

Did you take people who have never been on NSAIDs and are about to start NSAIDs? Did you take people who are already starting NSAIDs? And then a lot of these studies take people who have had ulcers, erosions, heal them, and then they enter them into the study. Perhaps they're at higher risk for current ulcers.

Other studies take people who didn't have any endoscopic lesions at all and enrolled those patients, perhaps those who are at lower risk for a current ulcer.

So I think it's very important when we look at these studies in the literature and when you design studies to take these kinds of things into account because I could show you studies that have different outcomes based on these different patient populations at the beginning.

And what are potential clinical endpoints? Just to digress and talk about this a little. Obviously symptoms such as pain and nausea, vomiting, we never talk about that, but the next slide will make the point that this is a very important problem to both practitioners and patients.

The clinically important and economically important ones are: bleeding, perforation, obstruction, any hospitalization for an ulcer, and certainly death. The problem, of course, with all of these in terms of designing studies is except for the symptomatic pain, nausea, vomiting, all of these endpoints are very low incidence and, therefore, the problem with doing studies.

I just want to make a quick pitch for

dyspepsia, what I think is a very important clinical endpoint, in your patients' mind, way more important than probably all of these other things. And certainly in terms of economic terms and quality of life terms, dyspepsia is an extremely important problem in practice.

There are major problems with doing studies of dyspepsia. There's a lack of correlation between symptoms and endoscopic findings. Both, as you know, are very common. And when you design a study, if you have a very low threshold for doing endoscopy, anybody who has dyspepsia, you'll find lots of ulcers, which may or may not be of any clinical significance. But if you make it very hard, you don't know what's right either.

I mean, I think in general, I would prefer a fairly difficult threshold for doing endoscopy related to symptoms. You can talk about that later, but pain interfering or stopping daily functions, pain not responding to anti-secretory therapy. Things such as this might be reasonable ways to go if you're designing that kind of study.

Now a quick work about *H. Pylori* and NSAIDs because *H. Pylori* has revolutionized gastroenterology. And we really have two important

causes of ulcer disease today. We have NSAIDs, and we have *H. Pylori*.

They seem to cause ulcers by two distinct mechanisms, but the big question is: Is there an interaction? And do we need to worry about that, for instance, when we're designing trials?

The first point I would like to make is my belief, summarized here on the title of this slide, is that the risk of NSAID-induced ulcer disease is increased in patients who already have an ulcer; for instance, due to *H. Pylori*. And I think there is circumstantial evidence to suggest this, past ulcer the most consistent risk factor for complicated ulcer disease, NSAIDs-induced, G used more than D used. That's gastric more than duodenal, for those of you who are into GI. But they have similar rates of complications of the two.

Also, because NSAID-associated complications occur most frequently in the first weeks of treatment, it may be that NSAIDs are just inducing complications or symptoms in patients who have clinically silent ulcers.

So I think most of us would agree that if you have an *H. Pylori* ulcer already, you very likely are at an increased risk to be taking NSAID. But most

people don't have an *H. Pylori* ulcer already. What about the vast number of people, a majority of the world's population, that has *H. Pylori* infection? What happens when you start that patient on an NSAID?

Well, this is an old slide, but it makes the point that there are lots of studies, including one from us, that suggest that, at least endoscopically, *H. Pylori* status doesn't really affect the development of NSAID-induced GI damage.

But then in the *Lancet* at the end of last year, there was a study, which was the first one to really directly address this question. And the question was: What if I take somebody about to start on an NSAID and I randomly assign them to get *H. Pylori* therapy or no *H. Pylori* therapy?

What they found is that when they gave *H. Pylori* therapy, there were fewer endoscopic ulcers occurring than in the group that did not get pretreatment *H. Pylori* therapy. So people took this to say, "Hey, maybe *H. Pylori* really is a risk factor."

Now, to really confuse matters, in the *New England Journal* papers, which just came out last week, it seemed clear that not only was *H. Pylori* not really a risk factor in the development of NSAIDs, but there

was a suggestion that was actually protected. In an unpublished ad I can't share with you, there are going to be more studies coming from Europe, which also raise the fact that *H. Pylori* is not a risk factor and, questionably, is even protected.

As an interesting aside, I'll mention that we have done a study that clearly, and as have others, shown that *H. Pylori* leads to an increase in prostaglandins. When you give an NSAID, those prostaglandin levels clearly fall, but they don't fall to as low a level as do people who don't start out with *H. Pylori* at the baseline, if you will. And so some have suggested that because you have got this buffer, if you will, of prostaglandin production there and your prostaglandin production doesn't fall as low, that *H. Pylori* may be protective in that way.

There's lot of disagreement about this, and it's a very controversial area. The bottom line is at this point in time, I don't think any of us would suggest screening all patients about to start NSAIDs for *H. Pylori*.

Now, the reason you're all here is about COX-1 and COX-2. I won't show this. Most people in the audience know more about this than I do.

There's very little, obviously, in the

literature about this in humans. Most of it is probably still proprietary. In a small study in gastroenterology, it was shown that in the human GI tract in a small number of people, that almost all of the prostaglandin synthetase was COX-1.

As you can see, there was virtually no COX being measured in terms of protein expression. This same group initially earlier had shown there was expression of COX-2 MRNA, however, in the human GI tract. And different species seem to be different. So there are differences from humans and nonhumans.

I'm not talking about any specific compounds that are still under investigation. So we don't care what this compound is but just to make the point that these COX-2 inhibitors do seem to not cause major or significant decreases in gastric mucosal prostaglandin synthesis. And that's obviously the basis for all of these trials.

Just in my last slides, I promise, I want to point out that there are a couple, at least a couple, three agents on the market already which also do not seem to decrease gastric prostaglandin production.

For instance, if we look at the non-acetylated salicylate Salsalate in orange, we can

see that over a one-week period, both placebo and Salsalate did not really decrease prostaglandin production while there was a significant decrease with aspirin.

In another study, just to show one that we did, with the drug Etodolac, as compared to placebo and Naproxen, you can also see that there was not a significant decrease in prostaglandin production. But there was a significant decrease with Naproxen.

So I'm ending here with my brief mention of COX-2 and, as a beginning, if you will, an introduction to what you guys are going to be talking about the rest of the day.

Thank you.

CHAIRMAN PETRI: I am going to request if you could stay at the microphone for questions and comments from the Committee members. And, if I might start, you didn't discuss the issue that was brought up in the open public hearing of wound healing.

DR. LAINE: In terms of COX-2 specifically or in general?

CHAIRMAN PETRI: Yes.

DR. LAINE: Well, wound healing I won't comment on. I'll comment on ulcers, though. And certainly there's a lot of debate. I'm not sure that

there is much in the humans.

I think it's been speculated that the speculation is: Is COX-2 necessary in healing ulcers; and, i.e., if you have COX-2 inhibition, will it inhibit ulcer healing and somehow interfere with that?

I don't know anything in humans about that, but there are probably people who know a lot more about COX-2 studies than I do that's been published. Certainly in animals, I believe that's been talked about and speculated.

Others have more information about that?

CHAIRMAN PETRI: Other questions from the Committee? Dr. Abramson?

MEMBER ABRAMSON: I was interested in the long-term endoscopic studies that you showed of 15 to 30 percent ulcers. I think it's six months and beyond.

How good were those studies in looking at the clinical symptoms of those patients in terms of dyspepsia or significant bleeding in that subset of patients?

DR. LAINE: I mean, virtually most of those studies are too small to really -- well, separate symptoms for a minute, but in terms of the complications like bleeding and perforation, they're

really too small to be very helpful in that because if you enter 100 patients in an arm, you might, just might, see somebody who has bleeding. And in general they've already gotten rid of people who have had that history.

So in general they're really not helpful at all. That's a problem. Most of these endoscopic studies, while big in terms of getting a few hundred people to go endoscopy every month or two, are small when you're talking about the development of these rather uncommon major complication endpoints.

MEMBER ABRAMSON: But, in other words, there were no clinically significant events that you could separate at 6 and 12 months in those 30 percent?

DR. LAINE: To my memory, no. And in terms of symptoms, you know, in general, again, the dyspepsia literature is really confusing. But most of the dyspepsia literature suggests that, in untreated patients at least, there does not appear to be a good correlation, only endoscopic lesions.

Now, it's interesting someone suggests that the endoscopic symptoms on anti-secretory therapy is a risk factor for the development of complications. And then others have suggested that, actually, some of those people aren't going to develop symptoms. And

that's actually bad.

So it gets very confusing. But I think if you can have some emphasis on anti-secretory therapy, someone suggested at least that that will increase the chance of developing a complication.

CHAIRMAN PETRI: Dr. Simon?

MEMBER SIMON: Loren, since you're here and you showed some data about measurement of gastric prostaglandins and you didn't define whether it was by biopsy or by gastric juice, could you comment on the utility based on what's known in the literature since there are conflicting pieces of data in the literature about the effects of various nonsteroidals presently available and those experimentally on either biopsy or gastric juice?

And what would be the component of the biopsy damage, if any, that might actually induce COX-1 or COX-2 under those circumstances?

DR. LAINE: It's hard to say. I don't know. I mean, I think most studies, those studies, for instance, do show a general relation between the fact that there is less gastric injury endoscopically and less prostaglandin inhibition.

But if you go through studies and really try to see is there a good correlation between the

prostaglandin level and the endoscopic injury, you really will find very weak correlation or no correlation.

So I don't know. I think they may be useful certainly in defining mechanisms. Whether they're truly useful in terms of defining clinical events, I don't know that they are.

MEMBER SIMON: I was just perhaps a little bit confused. If you're infected with *H. Pylori*, COX-2 is up-regulated in --

DR. LAINE: Well, that's actually somewhat controversial, too. There's not a lot of work on that. And, for instance, at our national GI meetings, there have been two abstracts who say yes and no.

It makes sense, you would think, that it should be and there is some evidence that it is found in *H. Pylori*, but there's going to be at least one paper that actually questions whether that's very important.

So I can tell you there's unpublished information suggesting to at least some people that you do see it in humans with *H. Pylori* infection, but it's not that well worked out, to my knowledge.

MEMBER SIMON: And one other question, Madam Chairman?

CHAIRMAN PETRI: Please?

MEMBER SIMON: Thank you.

In people that -- and I think you've done a lot of this work. When you biopsy a nonsteroidal ulcer and when you biopsy an *H. Pylori* ulcer, -- and you already showed some data about the general gastritis associated with that -- is there an implication that nonsteroidal ulcers are actually bland ulcers where there isn't actually inflammation in the local area associated with that?

DR. LAINE: Well, basically what happens is -- and there's some disagreement between us and some of the European groups in terms of the exact systology, but I think everybody would agree when you have an *H. Pylori* ulcer, the entire stomach in the United States in general has that inflammatory so long as you diffusely.

When you have an NSAID ulcer, right where you have the ulcer or the erosion, you know, I showed you those changes. And there's a very reactive epithelium right around there. And there certainly could be inflammatory cells right there where there's necrosis.

But as you go away from that, not the studies that we have done, if you were to go away from

that area, you would find back to the standard lack of gastritis unless the patient has *H. Pylori*. Don't forget a lot of people have *H. Pylori*. So there will be a background gastritis.

And we have actually looked at histology over time with baseline and then one and four weeks. What we found is that the underlying inflammation doesn't change at all in the stomach.

The only thing you find is just at those areas, you find those histologic abnormalities I showed at the areas of lesions but not at a distance in the uninvolved mucosa.

MEMBER SIMON: And just to extend that just one more second, if, then, that's true, do you believe that that's a function of the effect of nonsteroidals to decrease inflammation or do you think that that's something unique?

For example, if you put alcohol experimentally on the mucosa and you might cause damage, is there inflammation or not --

DR. LAINE: Well, it's actually the same with alcohol. The same is with NSAIDs or alcohol, which we have actually, at least in humans, looked at alcohol. And, again, what you see is at the area, you'll see these changes. But when you go away,

you'll see gastritis just if there happens to be *H. Pylori*-associated gastritis.

So it seems at least alcohol, at least in human model, if you will, you see these lesions but probably far away. If there's nothing endoscopically, usually you won't see anything. You may see something, but you don't see those inflammatory cell infiltrates like you do with *H. Pylori* in general.

CHAIRMAN PETRI: Dr. Liang?

MEMBER LIANG: I guess it's of interest to me who gets into these trials and who would be willing to have endoscopies and biopsies at this frequency. Are there studies of people who are eligible who refuse this invasive follow-up?

DR. LAINE: Invasive. That's an idea of --

MEMBER LIANG: Well, to give us an idea of how generalizable the results are.

DR. LAINE: Invasive for endoscopy, of course. Well, I mean, I don't know of any studies that looked at that. Certainly every study tells you about who is going to be excluded, but you don't know who is willing to undergo it at first.

I guess we as gastroenterologists don't find it I guess that hard to do that. You have to

remember that most of these volunteers are paid. Generally IRBs do not allow a very large amount of payment. So most of us probably wouldn't consider it enough for that alone to undergo endoscopy. So we do have the economic factor that is involved.

We do have people who are on NSAIDs who hear about all of these awful potential problems and want to know what's going on in their GI tract. I mean, I can't really discuss all the motivations. And I don't know of any clear studies that looked at that.

CHAIRMAN PETRI: Dr. Fernandez-Madrid?

MEMBER FERNANDEZ-MADRID: Would you like to elaborate on the clinical significance of the endoscopic evidence of mucosal bleeding with small dose of aspirin? Is there a correlation with measure of clinical events?

DR. LAINE: Well, in terms of the original studies where they looked at aspirin at one week and showed small amounts of mucosal bleeding, I don't know that there is likely -- I don't think that that really is associated or predictive of clinical events.

So I don't think that there is any evidence that that is clearly predictive of clinical events in terms of that initial one-day, two-day, three-day kind of thing.

And most of us believe that just the presence of those hemorrhages that I showed you in and of themselves are probably not really helpful or predictive of whether somebody is going to have a GI complication.

So I put much less stock myself in those, but I don't know that there's good information to tell us absolutely one way or the other.

CHAIRMAN PETRI: Can I ask you to follow up on that? If you had to pick the one thing on an endoscopy that is going to be predictive of a clinically important event, what is it? Is it the five-millimeter ulcer?

DR. LAINE: The ulcer with the major bleeding would probably be the --

(Laughter.)

DR. LAINE: But, short of that, it would be an ulcer. I mean, clearly of the three things I showed you, I would probably generally -- I don't have any problem with doing studies where you look at erosions as a kind of initial measure, but I think that most of us would agree that if you had to choose between those three, it's clearly an ulcer and --

CHAIRMAN PETRI: It's the five-millimeter ulcer, rather than the three?

DR. LAINE: Yes and no. I mean, certainly there's no doubt that a five -- well, there's no doubt. There's probably no doubt that five is going to be worse than three.

The larger the ulcer, the longer it takes to heal. If it did bleed, it's going to have a higher chance of re-bleeding. If it didn't bleed, you know, that isn't necessarily true.

So I think all of us would agree. I think most of us would think that depth is an important factor, though, because the issue we have, although it's non-quantifiable at this point, is you want to really make sure that that ulcer truly has significant depth, has real depth. That's perhaps more important, if you will.

Now, size probably has a rough correlation with depth as well. So --

CHAIRMAN PETRI: I thought you told us that right now the technology did not allow you to measure depth --

DR. LAINE: Oh, I agree.

CHAIRMAN PETRI: -- reproducibly.

DR. LAINE: It doesn't. What I'm saying is sometimes it's shallow. All of those things are very generalizable. I think, if you remember that

ulcer picture I showed you, sometimes when it's a big, deep ulcer, it's quite clear that that's a big, deep ulcer.

And other times when it's a three-millimeter, four-millimeter thing that just is ever so slightly depressed, there's no doubt in my mind, although it's very anecdotal. I'd be much more worried about that one-centimeter deep ulcer than I am about this three-millimeter thing that's very, very shallow and just barely meets my definition of an ulcer.

And, quite specifically, has anyone looked at whether there is dyspepsia in those patients who have a five-millimeter ulcer with a certain depth?

DR. LAINE: In terms of that specifically, no. I mean, certainly people have looked at ulcers as usually their definition being three millimeters and looked at the association with dyspepsia.

As I said, there are numbers all over the map, but usually in the untreated patient, I think we can say that there is a very poor correlation.

CHAIRMAN PETRI: Can you give us an idea what the ballpark would be for that correlation coefficient?

DR. LAINE: Well, it's just variable. I

mean, I really can't because in general what we're saying is that, let's say, 15 percent of people in some studies have daily dyspepsia, 30 percent of people have an ulcer. So there's such an overlap there.

CHAIRMAN PETRI: That's why I was trying to pin you down about whether the larger, deeper ulcer would have a higher correlation with symptoms.

DR. LAINE: To my knowledge, that isn't available. I don't know if any of the companies have information on that, but, to my knowledge, it isn't clearly available.

Most of us would anecdotally believe that the bigger ulcer is more likely to have symptoms, but I just don't know that we can say that based on the literature.

CHAIRMAN PETRI: So your advice to our Committee is that symptoms and five-millimeter ulcers are going to have to be separate endpoints?

DR. LAINE: Oh, I think very clearly that that would be the case, yes.

CHAIRMAN PETRI: Yes?

MEMBER KATONA: Dr. Laine, you have shown some very impressive picture of the stricture in the small bowel. What was the natural history? Did these

patients have ulcers, symptoms? Is it a late finding? Can you --

DR. LAINE: Clinically I'll say it's not very common. I mean, I've seen it just a couple of times with other people's experiences.

That picture and the best information is from a *New England Journal* article by Allison College, where they actually did autopsy studies looking at the development of stricture and diaphragms and showed that there was significantly more in the people who had been NSAID users or non-NSAID users. So it was really a nonclinical study.

So, again, anecdotally I think it's relatively uncommon, most likely because, although they may be there, they have to get down to a fairly significant point before they will be clinically manifest, the same with ulcers.

There's probably a lot more endoscopically observed damage in the small intestine. We just never look for it because we don't have means or it's a lot harder to get down there.

There are some interesting studies which have shown that if you take people who are iron-deficient, anemia, and actually look in there with special endoscopes, that a significant number of

them do have endoscopic lesions. And, actually, those can be -- the iron-deficient anemia can resolve with treatment with misoprostol, interestingly.

So it probably is a cause of iron-deficient anemia with some frequency. It's just not that well-recognized.

CHAIRMAN PETRI: Dr. Simon?

MEMBER SIMON: Since you're talking about that, Loren, could you expand a little bit on what is known about the biology of this particular lesion in the small and large bowel in that Mahmoud and colleagues have shown that it's not a prostaglandin-mediated event, others have claimed that it is related to prostaglandin inhibition.

Since we're going to be discussing issues that are relevant to that, could you tell us what you believe or what you believe is presently extent in the literature about what's understood about the ideology of these factors?

DR. LAINE: Of the strictures and ulcers?

MEMBER SIMON: Strictures and ulcers in the small and large bowel.

DR. LAINE: Got me. Actually, I really don't know for sure. I mean, I think in the small bowel, there's some suggestion that those that have an

enteropathic circulation may increase the risk of the development of small intestine and, i.e., keep going through and actually perhaps cause a local topical effect.

I mean, there are a lot of things speculated. I'm not sure that it's well enough known to say. There may be more information on things like the colitis, as I mentioned, and neoplasm, but in terms of the actual strictures, I just don't know that there's great information.

MEMBER SIMON: There have also been some reports, although we alluded to it before, about people with inflammatory bowel disease who then go on to perforate because they've been on nonsteroidals. And the claim was because that was an inhibition of COX-2. Could you comment on what we know about that?

DR. LAINE: To my knowledge, there are no good clinical studies to document that, but there are now some experimental models that suggest. And a lot of it, they're animal models in inflammatory bowel disease, which may or may not be analogous to human inflammatory bowel disease, that do suggest there at least that it is the COX-2 that is related to the exacerbation of the inflammatory bowel disease.

CHAIRMAN PETRI: May I ask you about

hepatic injury? It's something that will concern the rheumatologists on the Committee.

DR. LAINE: I must admit I really am a luminal gastroenterologist at our place. And we have literally -- so I probably don't know much more about it than you do.

MEMBER SIMON: Michelle, can I just make a comment about that?

CHAIRMAN PETRI: Yes and then Dr. Witter.

MEMBER SIMON: Because there actually is a large literature about that. And the largest one was a 625,000-patient study that was published in the *Archives of Internal Medicine*, 1994, that suggested that most nonsteroidals are actually extraordinarily safe regarding nonsteroidal toxicity. This is by Rodriguez.

And the suggestion was that the incidence is quite low and that one in particular, Suondac, was the more common cause, which corroborated previous literature from the drug case reports, adverse reaction case reports, from Australia that showed also that Suondac was the worst actor; colon colostasis in particular.

CHAIRMAN PETRI: Just to clarify my comment, we have a pediatric rheumatologist. Of

course, I'm a lupusologist. In rheumatology, we have these special subgroups of patients that might be at greater risk.

DR. LAINE: Right.

CHAIRMAN PETRI: Dr. Witter wanted to comment.

DR. WITTER: Loren, could you just comment about the incidence of clinical symptoms or significant clinical outcomes in children before you sit down?

DR. LAINE: Again, I don't know the information on that.

CHAIRMAN PETRI: Let me ask if Dr. Katona had a comment.

MEMBER KATONA: Just relating to the hepatic effect in pediatric rheumatology, the systemic onset JRH and the ones which have known to react with hepatic toxicity, probably even have underlying hepatic abnormality, which is not well-characterized.

But basically a very, very high percentage of them will develop hepatic side effects. And occasionally they even go into the -- so that's potentially very serious.

CHAIRMAN PETRI: Dr. Fernandez-Madrid?

MEMBER FERNANDEZ-MADRID: I have another

luminal question on the small bowel. I think the small bowel seems to be a potential target for interventions of serokines. Study patients, for instance, with rheumatoid arthritis to be treated with these new drugs and old drugs but most likely we'll need other second-line therapies or novel therapies, like collagen peptides, oral desensitization and so forth.

Is there any study looking, for instance, at animal models of rheumatoid arthritis that have been shown to improve with oral desensitization, with collagen peptides? Any of these nonsteroidals, although the new may inhibit this process?

DR. LAINE: To my knowledge, no. Just as an aside, it's interesting. When you look at the animal models of NSAIDs, the animals get much more disease in the small intestine. Generally they die. And they die of small intestinal disease and small intestinal perforation.

So it always raises the question: Is that truly analogous to the human situation because, although there is small bowel disease, it's not nearly as important as the stomach and duodenum? But in animals, it's really the small bowel disease that is what's killing the animals and is most devastating.

CHAIRMAN PETRI: Yes, Dr. Hyde?

DR. HYDE: Yes. One question that confronts us is how we can extrapolate from endoscopic studies. And towards that, can you comment on the degree to which endoscopic studies can distinguish between the currently available NSAIDs and then to what degree that might correlate with any nonclinical information we have?

DR. LAINE: Well, as I mentioned and just using those two last currently available ones, those two NSAIDs where studies showed there wasn't a decrease in prostaglandins also, at least endoscopically, do have less GI tract injury or very little GI tract injury in endoscopic studies. So I think that there's a kind of a gross association.

In terms of predicting and using endoscopic findings to predict clinical outcomes, is that what you're asking?

DR. HYDE: Well, I guess it has to do with the ability to differentiate between different ones, rather than a dose effect within a particular one, for example.

DR. LAINE: Right. I mean, right now I think, as I showed you, those studies do show that we can differentiate between, let's say, those two

studies with Salsalate and aspirin or Etodolac and Naproxen. And there was association.

Now, the problem is, although you have post-marketing surveys on these drugs and you can decide how much or little to believe the post-marketing survey, we don't have studies that really allow us to extrapolate directly from those endoscopic studies to show that those drugs clearly have less complications developing, although the only thing you could really do is look at a post-marketing survey and say: Is there a lower incidence of complications?

And you may show there that is true with those drugs, although I don't think it's really that clear. The only one, as I said, that I really think we have information on are the misoprostol studies, where we actually have the endoscopic studies and the clinical outcome study.

So I think we perhaps can extrapolate in those others, but I hesitate to say that we have clear information on allowing us to do that.

CHAIRMAN PETRI: I will allow questions from the audience if anyone wants to come to the microphone. Please introduce yourself.

DR. LAINE: Et tu, Dr. Chemian?

DR. CHEMIAN: Michael Chemian from the University of Washington.

Loren, that was a very nice review of the side effects of NSAIDs. You didn't mention too much about other GI toxicity. I'm interested in your comments. If you look at the large series of patients who come into the hospital GI bleeding, you find that about half of them are actually bleeding from some site other than an ulcer, --

DR. LAINE: Right.

DR. CHEMIAN: -- including lower GI and also for perforation. We find that probably 40 percent of perforations associated with NSAIDs are from the lower GI tract.

Would you agree that any further studies about new products should take into consideration not just ulcer bleeds and perforations but bleeds and perforations throughout the GI tract?

DR. LAINE: They were on my slides. I was talking quickly, of course. But, in any event, no. I absolutely agree that there -- that's why I mentioned the small bowel and the large bowel. I had up there diverticular hemorrhage and bleeding in some studies has increased.

There's no doubt that studies show that

bleeding is increased from non-ulcer and non-GI source, upper GI source, as well. So I agree with that. And I think it is certainly reasonable to include those.

The problem comes down to I think that those are even lower incidents probably that the gastric/duodenal ulcer bleeding. Certainly they occur, but you've got a real hodgepodge of different things going on.

Those studies, most of the time it's bleeding from a non-upper GI source or non-ulcer source, a lot of times not even defined. Certainly diverticulum is one of the major ones.

So I think it's very reasonable we need to worry about the whole GI tract. I think that the only problem is that those are going to be even lower likelihood. But I would agree that I would include them.

DR. CHEMIAN: If you speculate on why someone with a diverticulum in the colon would have a perforation, would put on an NSAID, you have to bring in ideas about healing of the colon. I think that's where the COX-2 issue comes to play. There are a lot of unknowns that we really need to explore.

DR. LAINE: I wasn't sure how that fit

into the diverticulum, though.

DR. CHEMIAN: Well, if COX-2s are involved in healing throughout the GI tract and in the colon and someone has a micro perforation from what they ate or something like that, then healing may be a very important way to keep that from becoming a clinically manifest perforation.

It's all speculation but I think at least has be to looked at.

DR. LAINE: I agree it's speculation. I think for the diverticulitis perforation, I would agree. For the diverticulid bleeding, I probably wouldn't because I don't think there's clear evidence of inflammation associated with the diverticulid bleeding. But for the diverticulitis perforation, I certainly think that's a reasonable thing to look at.

CHAIRMAN PETRI: Can I pin you down? Because one of the charges to this Committee is to help to design the perfect study. Do you think there should be studies with lower endoscopy?

DR. LAINE: No, I wouldn't have lower endoscopy because I think that would be too much, but I think if you're having an endpoint study, I think the point Michael is making is since we know there are other GI complications, we shouldn't necessarily just

say "ulcer bleeding," but we should say "GI bleeding as a whole" or "perforation as a whole," not just "ulcer perforation" or "ulcer bleeding." I think that's probably the point he's making, which may be a reasonable one to make.

CHAIRMAN PETRI: Dr. Welton?

DR. WELTON: Thank you. Andrew Welton from Baltimore.

Dr. Laine, I looked at the picture of the small bowel stricture and ulceration. I was indeed struck by the old proverb that a good picture is worth 1,000 words, but let me tell you your words are absolutely equally good to the picture.

It looked to me that this was reminiscent of what was seen over two decades ago with the use of enteric-coated potassium chloride. Are these data simply from enteric-coated aspirin wherein then the effect may have nothing to do with the prostaglandin issues or are these lesions seen with other agents, other than enteric-coated aspirin?

DR. LAINE: They're seen with other agents. And I agree. I don't know. There are some people who have speculated on the causes and whether it is a local effect with the repeated circulation of certain NSAIDs. As has been suggested, they are more

common in those, again, who are undergoing enteropathic circulation.

Whether they're caused by ulcers in the small intestine which then just stricture down with healing, I don't know the answer. Frankly, I'm not sure if anybody does here.

DR. WELTON: Thank you.

DR. LAINE: Thank you.

CHAIRMAN PETRI: Dr. Singh?

DR. SINGH: Kupar Singh from Stanford University.

That was an excellent presentation. I actually just have to make a couple of comments about some of the data that we have been putting together on GI bleeds.

We now have a prospective observation study of over 50,000 patient-years in patients with rheumatoid arthritis and over 20,000 patient-years in patients with osteoarthritis.

So while these are rheumatoid and osteoarthritis patients and, therefore, data may or may not be applicable to patients who do not have these diseases, we have assembled a database of over 600 GI hospitalizations for a wide variety.

And when I started looking at some of the

information that you're talking about, what happens to bleeds not from peptic ulcers; that is, their lowering the standard pathology, we presented an abstract at the last GI meeting, in fact, -- and Dr. Jennifer LaPoulus is writing it up -- where we found that, yes, indeed, as Dr. Chemian was saying, when you look at bleeds, only in about half the cases were people able to identify where the blood was coming from. And so ulcer bleed is not just the only thing. I would agree completely with that being a rheumatologist that you would need to look beyond the ulcer bleed.

The second thing that we found, of course, when we listed out all our causes -- and because we had big numbers, we were able to separate out what you would consider as a lower GI pathology -- we found that in general while they were at the odds ratio, the relative risk for the upper GI pathology, ulcer bleeds, and perforations were in the range of about eight to nine, small interstitial complications also seemed to occur more prominently.

There were a couple of things that, surprisingly, occurred less commonly with people with NSAIDs. And one of them actually made it past the statistically significant barrier, and that was hospitalizations for diverticulitis.

It seems like that NSAIDs not only do not precipitate diverticulitis but may because of the anti-inflammatory activity do something to diverticulitis to reduce the symptoms of diverticulitis. And people were not getting hospitalized for diverticulitis.

Similarly, while the lower interstitial ulcers and pathologies seem to be increased, we couldn't demonstrate much in terms of the strictures. And one of the hypotheses that our gastroenterologists said it's probably the strictures because of the inflammation and these drugs are causing less inflammation.

I would be happy to share that data with you once --

DR. LAINE: About three weeks.

DR. SINGH: Yes, there with us next week -- actually, in a couple of weeks.

Then the other thing that I wanted to point out was this whole business about tieing to the event as to whether NSAID bleeds occur more commonly in the first few months or the first few weeks or they occur more commonly later on or is there any correlation at all?

Now, epidemiologists would define the

studies that are done in the NSAID as two kinds: a case-controlled study and a cohort study. Most of the data; in fact, all of the data, that show that bleeds occur early on come from case-controlled studies. And Dr. Gabriel denoted as did Dr. Clayborne Mardiet in some of her articles that these particular studies are not designed to show that information.

I mean, what is a case-controlled study? A case-controlled study is you identify a complication. Let's say you identify people with bleeds. And then you compare them with people who do not have bleeds and go back and see what these guys were doing.

And the case-controlled studies have many biases, including the call bias and things like that. And they're not really truly designed to show the time sequence of events.

To do that, you need a cohort study, which means take a large number of people, follow them up for a long period of time, identify exactly when a bleed occurs, and then do analysis that takes into account censoring of data, do a couple of months of analysis.

We did that. We did that in over 3,000 patients. And we had data going up to over 13 years.

And when we did that, covered data going up to over 13 years, the hazard rate of the negative log of this distribution function, which is the real quantification representative of the hazard rate, it was virtually a straight line.

All the other studies that have used similar methodologies, the MUCOSA study when you look at the placebo rate had a straight line. John Paraida, the data that you showed, the Bayside data that's come from England that have used similar censored data analysis studies have shown that indeed the risk of NSAID bleeds remains constant with time. If anything, it tends to go up a little bit because of the age. And some of the earlier data that we have about early bleeds may just be an artifact of the way that the studies were done and analyzed.

A final thing as to can you take the responsive endoscopic ulcer reduction to mean anything significant clinically, that obviously is a point of big debate. And I would urge people to read Dr. Clayborne Mardiet's article that was published in *Arthritis and Rheumatism* a couple of months ago.

The article actually was on the cost-effectiveness of misoprostol, but they wrote a very nice discussion on: Can you generalize from

endoscopy ulcer healings to clinically significant events?

Well, clearly, as Chris Hawkey says in his *New England Journal* article, if you reduce the incidence of endoscopic ulcers dramatically, you are probably going to see some effect in reduction of clinically significant complications because it's hard to believe that a reduction in ulcers would only occur of ulcers that do not cause complications.

On the other hand, the effect or the magnitude of the effect is still unknown. We know that in all the misoprostol, for example, endoscopic studies, misoprostol reduces the incidence of endoscopic ulcers by over 98 percent, 95, 98, 97 percent. Some of the data that you showed also showed similar reductions.

Yet, with the clinical complications in the MUCOSA study, it only reduces that by about 40 percent. So while there is some correlation, it probably is not a one to one correlation.

DR. LAINE: Qualitative, rather than quantitative.

DR. SINGH: Qualitative and quantitative. Qualitatively, yes, I would agree with that.

The same thing applies to: Can you use

endoscopic data to rank NSAIDs? And I agree with your point that you would need large enough studies to do that, although we have shown from our own data and from other data that the two NSAIDs that you were talking about and the other NSAID, where there is a lower incidence of endoscopic ulcers, do indeed translate into clinically and statistically significant superiority in terms of lower complications of the gastric internal kind when you look in several thousand patients after they release.

CHAIRMAN PETRI: Thank you.

We're going to Dr. Abramson.

MEMBER ABRAMSON: I'd like to follow up on a portion of that comment. You entered data that I wasn't aware of today. We both kind of dismissed early endoscopy studies as being predictive of clinically important events, and you extended it out to 6 or 12 months, where there wasn't the correlation.

Can you make a case as to why since we now do not have data that there is no predictive value for these regularized endoscopic studies, why they should be incorporated into outcome analysis at all or as opposed to having endoscopies that are indicated by certain criteria?

DR. LAINE: Well, a couple of points. I

mean, you can do both, I think. One thing I would agree with is that I wouldn't probably want to do a very early endoscopy. I don't think there's a need.

You know, the more endoscopies you do, the more lesions you're going to find. So if you do an endoscopy every two weeks you'll find a lot of lesions because they come and go.

So you probably don't want to do a million endoscopies, and you probably don't want to do one too early, certainly in the first few weeks because you're not sure what that means since everybody is going to get some damage.

The second thing is I think you can certainly argue for two separate trials. You can have an endoscopic trial, and you can have a clinical outcome trial. And the clinical outcome trial really in a large, large study doesn't have to require endoscopies at all because it's two different issues, I think. One is an endoscopic ulcer issue, and one is a clinical outcome issue.

Now, you can combine those in one study if you want or you can use two separate trials. I don't think you have to do -- I would separate them out as endoscopic ulcers, on one hand, and the clinically important complication, on the other.

CHAIRMAN PETRI: Although we still want to know: What are the predictors of the clinically important outcomes. Without an endoscopy in the asymptomatic phase, how would you know what the predictors were?

DR. LAINE: I agree. That's attractive in terms of advancing science, I agree. The only question, of course, is -- and I have no problem with it. I mean, it becomes a practical issue.

If you had to do a study of 10,000 people or, as the MUCOSA trial, 20,000 people and you're going to endoscope them at baseline and every couple of months, it may become prohibitive. And, as was mentioned by one of your members, you can get a lot of people to do endoscopy but probably can't get everybody to do endoscopy. And that's certainly going to be a turnoff to entry into the study.

So I think there are potential problems with that. I'm not saying it's not doable. In an ideal world, I think that would be nice.

CHAIRMAN PETRI: Dr. Yocum?

MEMBER YOCUM: I was very interested in your data on low-dose aspirin. We have a lot of patients now taking that. There are a lot of available over-the-counter nonsteroidals. We know

that gastric complications seem to be increased for rheumatoid arthritis or there's likely to be this sort of activity.

And since we are discussing the perfect study, should, in fact, new nonsteroidals have included some sort of study to look at the potential of concomitant low-dose aspirin or other nonsteroidals, either endoscopy or clinical outcome?

DR. LAINE: Yes. It's an interesting question. There are studies that suggest, as you know, more than one NSAID increases the risk. And that makes sense. It's a problem every time you do studies like this or other studies. Do you include people on bachelor prophylaxis doses? And obviously I can argue either way probably quite nicely.

So I think it's a real-world phenomenon. So I think it's not inappropriate. You're going to see more and more people obviously on bachelor prophylaxis with aspirin. And in the future you may see people on colorectal neoplasm prophylaxis with nonsteroidals. That's also very likely. So I think it's only going to be increasing.

So it's not an unreasonable side thing, although I think I wouldn't think it's nearly as important as just the initial decision about drugs and

how they work in general.

MEMBER YOCUM: But we really don't know this complication rate. I mean, it must be rather worrisome. At least I would be.

DR. LAINE: No. I mean, that it will certainly increase. Somebody on 81 or 325 of aspirin and an NSAID for another reason certainly is going to increase. And I think the other important point that you make is certainly COX-2 inhibitors are not going to be useful for vascular prophylaxis. So you're still going to have your patients on aspirin for that reason.

So I think we need to keep that in mind. I would agree.

CHAIRMAN PETRI: Dr. Simon? And then there will be a question from the audience.

MEMBER SIMON: To take your comments before, Loren, to its obvious conclusion and for the sake of argument, why in the world do we do endoscopy trials at all if, in fact, they're not predictive, if, in fact, we can't know what the real outcome will be, other than the costs associated with it both from the point of view of gastroenterology being supportive as a field --

(Laughter.)

DR. LAINE: Which is not unimportant.

MEMBER SIMON: But, in reality, then, given the discussion we just had with what Steve just asked and what we've heard so far, what truly in a design of an ideal study does endoscopy provide us other than raw number that tell us something about ulcers but don't tell us anything about, really, the important clinical outcomes.

DR. LAINE: Tradition.

MEMBER SIMON: Okay.

DR. LAINE: No. First of all, I think you can -- I mean, you have to define what you want to determine. Certainly if you're worried about clinical outcome, one can, as I said, make a clinical argument to do just a clinical outcome study without endoscopy.

Certainly you gather important information when you do endoscopy, but I agree. You study what you care about. And you can certainly make an argument for that.

I think the other argument would be over the years, certainly the agency and most people in the field have assumed that if you don't get ulcers, you get less ulcers, you don't get complications.

And certainly if you totally prevent ulcers, you're going to totally prevent complications.

On the other hand, a purist will say, "Well, maybe those ulcers are different from the complicated ulcers that we get and that there's absolutely no association."

I think in the past people have accepted that there probably is some association, although it was really based more on intuition than literature. And I think that's clearly why we've done it in the past.

And clearly it's so prohibitive perhaps to do those studies that it becomes difficult as well.

CHAIRMAN PETRI: I believe there's a question from the audience. Please go to the microphone and identify yourself.

DR. SILVERSTEIN: My name is Fred Silverstein. I'm a gastroenterologist from Seattle, and I've been a consultant to Searle.

I'd like to make one comment addressing this very important issue about the role of the endoscopic study because I really agree with what Loren has said.

It certainly is not possible to take every putative protective agent into a MUCOSA-type trial with 8,800 patients. It just isn't possible. And endoscopic trials are a very good way to look at the

incidence of damage, looking at the ulcer as the endpoint, whether it's a three or five-millimeter ulcer.

So endoscopic studies are tractable studies that can be done. I certainly agree with Loren that a one or two-day study is not predictive, but a one, two, and three-month study would appear to be predictive of injury and tell us how a particular agent, a new NSAID, a COX-2 inhibitor, or a protective agent, reduces the likelihood of ulceration.

Ten years ago at an FDA advisory meeting, we discussed the relevance of reduction in ulcer injury versus complication rate. And it was stated then by the gastroenterologist that although the hypothesis is that if you lower the ulceration rate from 20 percent to 2 percent, you can't be sure that you're going to lower the complication rate.

And that's why the MUCOSA study was done because it finally bit the bullet and said: We've got to look at this very complicated long-term study to see if it really does decrease it. In fact, it about halved it. It about halved the incidence of ulcers.

The three-month endoscopic studies with misoprostol that did show a greater reduction in ulcers, the comment was made that: Therefore, it

doesn't predict what's going to happen clinically to important outcome. But, in fact, there have been 2 endoscopic studies going 6 to 12 months that have also shown about a halving of the incidence of ulcers.

So what I'm saying is the endoscopic study showed about a 50 percent reduction and a clinical outcome study showed about a 50 percent reduction. So it gives us some degree of confidence that, in fact, an endoscopic study, at least for these agents that have been well-studied, is predictable of clinical outcome.

Now, I think when a new agent comes along, it's relevant to ask if there will be endoscopic studies, which can be well-controlled, change dose, change frequency, do all the different things we want to do, and then ultimately look at the clinical outcome because that is, in fact, as Loren said, the part that's really important to the patient and to the physician, not only symptoms, but the incidence of a complication.

But I do think that probably the thing that interested me the most about the mucosal trial, which took thousands of hours of work by a whole coterie of people, is that it did validate the fact that the endoscopic trials do roughly predict what

happens clinically.

CHAIRMAN PETRI: Can you define "roughly" because obviously the Committee is hearing different things?

(Laughter.)

DR. SILVERSTEIN: Right. Well, there were two studies, as Loren said, that have looked at --

DR. LAINE: One of the things that all of us have said -- I mean, all three people have actually said the same thing.

DR. SILVERSTEIN: Right.

DR. LAINE: It's just a matter of being sure about that degree of decrease. That's why I was using the word "qualitatively," instead of "quantitatively."

Go ahead. I'm sorry.

DR. SILVERSTEIN: Right. Well, the two long-term trials, one by Elliott and one by Geis, showed that with misoprostol, there was a halving in the incidence of ulceration.

So if you looked at people over a year, they had approximately 15 percent ulcerations on misoprostol plus an NSAID and 30 percent on a placebo plus an NSAID, so approximately a halving.

In the MUCOSA trial, we found that about

one percent of people on NSAIDs had one of these complications in six months and approximately .5 percent had a complication if they were on the NSAID plus misoprostol. There was, in fact, a 40-something percent reduction.

So it was comparable. It was a reduction from 30 percent to 15 percent in a long-term endoscopic study and from 1 percent to .5 percent in an outcome study.

CHAIRMAN PETRI: But is the reduction always within that same subpopulation? So, in other words, do you ever see the clinically important complications in patients who endoscopically didn't have the five-millimeter ulcer with a certain depth?

DR. SILVERSTEIN: Well, these are really different studies. As Loren said, the outcome studies aren't done necessarily the same way. And, in fact, endoscopy was not a prerequisite for the MUCOSA study. We, rather, followed these 8,800 patients and in a blinded fashion when an event occurred tried to look at it clinically and determine whether it was an important clinical event for the patient.

And we looked at bleeding, perforation, and obstruction, but, of course, we kept track of all the other complications that Dr. Chemian, Loren, and

Dr. Singh have mentioned.

So it's a little hard to be exactly sure whether you can identify endoscopically the patient who will be at risk of an adverse complication, but the magnitude of the change was the same.

DR. LAINE: Let me just ask: In the three-month studies, the magnitude of the decrease in endoscopic ulcers was greater.

DR. SILVERSTEIN: Right. But I'm trying to explain that isn't a total disparity because you had said that you can't really predict, that the endoscopic studies aren't predictive. In fact, they are predictive of a reduction in injury.

They're a very important part of this, but we all feel that you should go on to a clinical outcome analysis as well to show that this part of it is reduced.

CHAIRMAN PETRI: Dr. Liang is going to redefine my question.

MEMBER LIANG: We're asking a different question. At the patient level --

CHAIRMAN PETRI: By patient.

MEMBER LIANG: -- by patient, if you see a little ulcer, does that person eventually go on to having a clinically important event? You're telling

us group data in different studies, which is not what we're asking.

DR. LAINE: Rarely. Rarely.

MEMBER LIANG: So the answer is that it's not predictive in our sense of the individual patient.

DR. LAINE: It depends on --

MEMBER LIANG: You say that endpoint correlates with findings done by other surrogates. And that's okay, but it's not what we're asking.

DR. LAINE: I mean, it does in the sense of as compared -- sorry for interrupting -- to no ulcer. So if that person has a small ulcer versus no ulcer, what Fred is saying is that there was evidence that that can be --

MEMBER LIANG: Did all patients with clinically important event have a little divot?

DR. LAINE: Anybody who has an ulcer bleed has to start with a divot.

MEMBER LIANG: Do we know that?

DR. LAINE: Well, because you can't have an ulcer if you don't start. There has to be a break.

MEMBER LIANG: No, no. I'm talking about a clinically important event. You know, we say that these ulcerations can come and go. What we know: The people who got admitted for GI bleeds, did they have

--

DR. LAINE: Any ulcer that's complicated, a bleeding ulcer, has to start as an erosion.

MEMBER LIANG: I understand that, but --

CHAIRMAN PETRI: I thought we just heard that 50 percent of the GI bleeds, you don't know where they're bleeding from.

DR. LAINE: But that's separate, and that's different. That's not an ulcer bleed, though. That's a different issue. In addition, what he's saying is there are small intestinal and colonic bleeds that aren't from gastric or duodenal ulcers. And 50 percent may be higher than most people would suggest.

MEMBER LIANG: I think your answer, the way I hear it, is that it's not predictive in the individual patient.

DR. LAINE: Well, certainly not in the individual patient. Absolutely true.

MEMBER LIANG: Okay.

PARTICIPANT: One comment. I learned from Loren about seven years ago that the appearance of the ulcer is predictive potentially, just to clarify that.

Not all ulcers are the same. And if you happen to look at an ulcer that's got a black spot or

it's got a protruding vessel or it's got an inherent clot, the endoscopist would then say, "This is an ulcer which has a higher likelihood of causing bleeding or causing re-bleeding."

MEMBER LIANG: That in some parlance is sort of a substitution game. I mean, that's already a bleed. That's predicting a bleed. You know, there's some circularity, I think.

DR. LAINE: Well, he's really talking about people who have bled previously haven't -- there are endoscopic features that --

MEMBER LIANG: I know. This is not a prediction that someone who bleeds bleeds.

CHAIRMAN PETRI: We have to introduce everybody before you talk. Dr. Singh?

DR. SINGH: I think what you're trying to say is that: Has there been a study where they have done endoscopy and found ulcers or no ulcers in given patients and seen also the different sizes, 20-millimeter, 3-millimeter, 5-millimeter, with that, without that, with bleeders, without bleeders, and then followed those patients to see how many of them actually got a clinical complication? I think that's the question you're asking.

I don't think there's such a study. I

mean, I don't know.

MEMBER LIANG: I think that is the question, and I --

CHAIRMAN PETRI: Is the reason that the patients are then withdrawn from the NSAID when that's found? No one is --

DR. LAINE: They're treated.

DR. SINGH: Either they're treated or these are endoscopic studies which are shot-down studies. And they don't then basically follow patients.

I believe in an ideal world you would want to do something like that, just like what you were suggesting, that you would want an answer to that question, that: What is the characteristic of an endoscopic ulcer that might tell you that these are the ulcers that we need to look at? And it's the reduction in these ulcers that is clinically important.

DR. LAINE: But realistically you could never do such a study because --

DR. SINGH: That's true.

DR. LAINE: -- if you have a patient who is on NSAIDs, you find an ulcer endoscopically, and you're going to continue NSAIDs in that patient, I

find it hard to believe that any IRB would ever accept such a study.

DR. SINGH: You're right. You're right. That is a problem.

DR. LAINE: So, by definition, we can't really do that.

MEMBER LIANG: I don't think that's true.

DR. LAINE: Somebody has an ulcer, and you continue on the NSAIDs with no therapy?

MEMBER LIANG: You told us that there's data that they come and go, with or without treatment.

DR. LAINE: They do come and go, but if you're going to continue the NSAID with no treatment, I would find it unlikely that you're going to continue NSAID, no treatment, in somebody who has a documented ulcer because of the risk of bleeding --

CHAIRMAN PETRI: But you've just told us you don't know what that risk is.

DR. LAINE: Well, we know that there is some risk. Even if we just take the fact that there's a half a percent rate of a year of bleeding and we take the fact that there's 30 percent of people who have an ulcer, we could say there's a one in -- I mean, we shouldn't really be doing that, but we can say there's a one in 60 chance or one in 100 chance if

that patient has an ulcer that they're going to bleed.

CHAIRMAN PETRI: Dr. Abramson?

MEMBER ABRAMSON: I guess the problem seems to be that all of these studies, endoscopic studies, are by their nature underpowered because if you look at the numbers you just mentioned, 30 percent are going to have ulcers but only less than one percent will bleed clinically. Then, even in a subgroup that has ulcerations less than five percent or three percent are going to have a clinically important outcome. Then we don't even know if it's from that group that has the peptic ulcer disease to begin with.

So the question I'm asking is: Is it feasible? So, therefore, it seems to me to answer this question, which is a reasonable question, we need large studies to see if there is predictive value.

But up to now, we haven't had endoscopic studies that are powered enough to look at those small numbers. I guess it's a feasibility issue.

MEMBER LIANG: You're absolutely right. Certainly these studies are all powered to demonstrate differences in endoscopic ulcers. None of them are powered endoscopic studies to look at clinically important outcomes because those are very low

incidence outcomes. And that's been the problem. And that's why --

MEMBER ABRAMSON: One in 30 are going to have an outcome of the endoscopic ulcers.

MEMBER LIANG: Of people who have an ulcer, perhaps one in 30, but one in 100 may have a bad ulcer.

CHAIRMAN PETRI: Dr. Chemian?

DR. CHEMIAN: I'd just like to point out I think the endoscopic studies are a screening test or a way to look for drugs and their effect on GI mucosa, but they're not an outcome. I mean, they're clearly not an outcome.

People come off the studies once a defect is seen. And they're usually done in people who are not even at high risk for ulcers. Most of these studies have been done in patients who are excluded if they've had a history of an ulcer complication.

So I view these endoscopic studies as a screening test to see if a new drug maybe has less GI toxicity, but they certainly shouldn't substitute for outcome studies.

You know, endoscopy is something we look in the stomach and duodenum, but, again, increasingly we find these drugs are associated with complications

throughout the GI tract. And we don't look at those in any of these endoscopic studies.

CHAIRMAN PETRI: Your point is well-taken. The Committee has been asking whether endoscopic studies might be a surrogate for clinically important outcomes. And this is obviously an important question in terms of length of studies, cost of studies, number of patients that have to be in a study.

Next question from the audience? Always please identify yourself.

DR. GAGWAR: Norang Gagwar from the University of Connecticut.

I just wanted to share some information with the Committee. What you are trying to ask, Dr. Liang, is natural history of GI bleeding in patients who may or may not have ulcer disease.

And, actually, Loren, I would like to point out there was a study that we published two years ago in patients with rheumatoid arthritis we see having gastric ulcer, taking four grams of aspirin per day and treated with misoprostol and placebo.

Of those 300 patients, there were only 2 complications followed for 3 months, suggesting that these data in patients with ulcer disease on placebo receiving large dosages of aspirin.

To look at complication rate I think is very variable and unpredictable as to in a given patient, if anyone can ever predict that this is a patient with ulcer who will bleed six months, three months, or a year from now, that sort of study would be a real coup for the Committee to perform and ask someone to do.

Thank you.

CHAIRMAN PETRI: Let me ask our FDA representatives if they had other comments or questions they wanted to bring up at this time.

(No response.)

CHAIRMAN PETRI: Okay. Well, I think we'll let Dr. Laine have a rest. Thank you.

We're now going to move on to another part of the body. Dr. Kevin McConnell is going to discuss the nephrology concerns with NSAIDs.

MEMBER McCONNELL: Thank you very much. My discussion is going to be a bit more broad. And I'm actually going to talk about the NSAIDs within the overall context of analgesia for several reasons, primarily most because many of the studies have not necessarily completely distinguished between whether someone was on acetaminophen or whether they're on a classic NSAID. Secondly, I think the birth of renal

epidemiology really comes about in this field.

It's well-known and well-established that prostaglandins play a role within the kidney. Both COX-1 and COX-2 exist within the kidney. COX-1 has a more constitutive housekeeping role and is expressed largely in the medulla, the collecting tubule, and medullary interstitial cells. COX-2, on the other hand, is expressed within the cortical collecting duct and particularly the cells of maculodensity.

Just to make one other comment, in the kidney, the primary prostaglandin is PGE_2. Thromboxane and PGF_2 have vasoconstrictory functions primarily; whereas, PGE_2 and PGI_2 have vasovillitory effects. There's not a whole lot of work done with PGD_2 and I think probably not terribly important.

Within the kidney, the prostaglandins have a variety of actions. One of its most important functions is to antagonize the hydroothmotic functions of antidiuretic hormones.

Secondly, it antagonizes vasoconstriction; third, maintains renal blood flow and, consequently, GFR; fourth, to increase renal secretion; and, finally, to increase sodium excretion.

Despite this, in the basal state, there's clearly relatively little function to prostaglandins.

It was because of its low-rate secretion and also because of metabolism, prostaglandins within the circulation.

There are, however, important modulatory roles in pathogenic states. I think it's also worthwhile pointing out that prostaglandin synthesis is increased by endotensin 2, norepinephrine, adiage, and endothelin. Those entities would be important in these pathogenic states. Therefore, the overall function of prostaglandins is in a counter-regulatory or protective function.

I want to make some basic general definitions. The first is that classical analgesic nephropathy. These are largely borne out of studies in Melbourne and Brisbane and Belgium in which there was habitual consumption of at least two anti-pyretic agents, very often including phenacetin.

Classically, renal papillary necrosis is seen, chronic interstitial nephritis. And there was the insidious and progressive development of renal insufficiency.

Secondly, there is nonsteroidal-related neuropathy. And I'll cover that in a bit more depth; and then, finally, the possible role that acetaminophen may play in the development of

end-stage, which I would say would be synonymous with dialysis-dependent renal disease.

The diagnosis of analgesic neuropathy. Historically, this had been defined as regular usage totaling greater than one to two grams in a lifetime.

I think more recently there's been interest in now imaging these people to try and make a diagnosis consistent with analgesic neuropathy. That would include CT imaging, non-contrast CT imaging of the kidney with bumpy contours. This has a specificity of greater than 90 percent in the studies, decreased renal length, which is more sensitive, and the presence of papillary calcification.

You may recall there was a very nice recent review of this in the *New England Journal* showing the appearance by CT scan and looking at the measurements. They put this measurement here, sort of the length and the width of the kidney to define whether there was a decrease in renal length, and then also the CT appearance of these indentations. Clearly the kidney becomes quite shrunken in these situations as well.

Here are several cases taken from people with presumed analgesic necropathy who had been on analgesics for a long period of time. And you see

here these characteristic papillary calcification, which would be a hallmark of interstitial disease.

In addition, typically one would find sterile pyuria and then obviously an appropriate clinical context, which would include chronic pain, hypochondriasis, very often substance abuse. There may be some bias, but in the studies, there is generally a five to one ratio for women to men.

Turning now to nonsteroidal nephrotoxicity, this in sort of decreasing order of frequency would be what one would generally observe, including electrolyte disorders; acute renal failure; tubulointerstitial nephritis and nephrotic syndrome; papillary necrosis; and, finally, hypertension. And I'll talk about each of these.

The most common disorders are those fluid and electrolyte disorders. Sodium retention edema is seen in approximately three to five percent of patients on nonsteroidals. This impairment of prostaglandin synthesis occurs in distal tubule. And it results in excess sodium reabsorption. Typically the weight gain is on the order of one to two kilograms and is not excessive.

Secondly, hyperkalemia is seen. This is a consequence of reduced renal stimulation and

availability of aldosterone. So what one would classically see is sort of hypogland, hypoaldosterone renal tubular acidosis.

A second reason for this would be diminished salt presentation to the distal tubule. We have to present on the order of 10 to 25 milliequivalents over the course of the day of sodium to the distal tubule to effectively dump potassium through lumenal channels into the final urine.

This is usually restricted to an at-risk population, the older patient, the more volume-restricted patient. Indomethacin may be somewhat different in that it may have an effect where it directly inhibits the cellular uptake of potassium.

I would also mention that hyponutrenia can commonly be seen in some patients who are on nonsteroidals. And this can be quite profound. For example, for patients with typical syndrome of FIAHD, syndrome of inappropriate ADH release, would commonly come in with a serum sodium of 117, 118, or 120. These patients, a patient who is volume-restricted or might have congestive heart failure or on an ACE inhibitor, they come in with serum sodiums beneath 110.

Obviously from the standpoint of

nephrologists, a major concern is that of acute renal failure in association with the nonsteroidal agents. This typically involves higher doses. It may follow either an oliguric or a non-oliguric course. And I think as nephrologists, you would generally say a non-oliguric course would be preferable to an oliguric course in terms of ultimate function.

Even in those patients who recover their renal function, it's not necessary back to their baseline. And they may be left with 25 to 50 percent reduction in baseline.

Typically it is reversible within several days of discontinuing the nonsteroidal agent. And there are a number of predisposing conditions.

Most important would be that of underlying renal disease. Secondly would be that of volume depletion, either as the resultant patient being concurrently on diuretics, having nephrotic syndrome, patient cirrhosis ascites, and those patients with congestive heart failure.

Taking those latter two incidents, those patients with cirrhosis and those patients with congestive heart failure, this has not typically been seen if they're presenting reasonable amounts of sodium to the distal tubule gap, they're presenting

something on the order of 10 to 25 milliequivalents. Those patients can take something typically on the order of 200-400 milligrams of something like Motrin and not be affected.

But in those patients who are sodium-avid, meaning they are reclaiming sodium throughout the kidney, particularly in the distal tubule, and they have less than 20 milliequivalents in the distal urine, they would be at high risk.

These are the features of this unusual entity of tubulointerstitial nephritis. It develops over a variable period of time and can occur within a single dose, more commonly develops within several weeks to several months of starting the nonsteroidal agent, but is marked by a heavy proteinuria. Nephrotic range is a proteinuria. It follows a non-oliguric course.

Eosinophils, both peripherally and in the urine, are uncommon, which makes it somewhat distinctive from what one commonly would think interstitial nephritis should reveal.

There is a t-cell interstitial infiltrate, no b-cells, and there is minimal change disease. That is infusion of the foot processes. This would be, again, a very uncommon lesion to see that coexists in

its interstitial infiltrates and minimal change disease. And, finally, the role of steroids in this particular entity is unclear.

In a small minority of patients, hypertension is seen with the nonsteroidals. This is usually a modest increase, five to seven millimeters of mercury. Patients on beta blockers, ACE inhibitors, and diuretics appear to be most at risk. There is some data that patients on potassium channel blockers may be at less risk. Finally, there is also some small amount of data supporting that the elderly and African Americans may be more at risk.

Turning now just a little bit more globally in the context of analgesic necropathy, as I mentioned at the outset, this is sort of really the birth of renal epidemiology.

Nineteen fifty's epidemiologic studies reveal an association between the phytyl ingestion of phenacetin-containing analgesics in renal failure secondary to what was called chronic pyelonephritis.

Despite the withdrawal of phenacetin from most markets, the prevalence of renal failure due to this entity is not zero. I think, for that reason, there was an interest in whether there may be other analgesics that cause this.

I'll now turn to acetaminophen nephrotoxicity. Again, I've included this within the discussion of nonsteroidals because many of the studies don't necessarily distinguish between one of the other or, rather, they were done as case-controlled studies, which asked people about their usage of a variety of analgesic agents.

And I think as well there may have -- we frequently tell people who have some element of renal insufficiency not to take classic nonsteroidals, in fact, and tell them, instead, to take acetaminophen. So we may be creating a disease entity.

There are three case-controlled studies which examined whether acetaminophen played a role in end-stage renal disease. In one study, a study by Pommer, this was an ESRD of patient population drawn from the general population but compared with hospitalized control patients.

In a second study, Sandler, hospitalized patients with end-stage renal disease were compared to controls from the general population. In this particular study, I don't recall that there was a linear increase in the incidence of end-stage renal disease with increasing analgesic use. In these two studies, heavier intake of acetaminophen was felt to

increase the odds.

In what is probably the most important study regarding this entity, that of Perneger, patients who had been on either aspirin and some other agent but not acetaminophen, acetaminophen but not aspirin, nonsteroidals, and then some patients who had been on phenacetin before phenacetin was withdrawn from the market, were looked at.

This is a case-controlled study of analgesics, either singularly or together. Cases were drawn from a popular patient base registry here in the Mid-Atlantic area of patients with end-stage renal disease. Controls were selected through random phone dialing in the same area.

Accumulative intake of more than 1,000 pills doubled the odds of end-stage renal disease. The odds of end-stage renal disease were increased in a variety of patients with underlying renal disease; patients with diabetic necropathy, for example.

A dose response rating existed for acetaminophen. And, finally, there was a J-shaped response which existed for aspirin and nonsteroidals. For example, those patients who had been taking somewhere between 100 and 400 tablets of nonsteroidals had less risk with them on the ESRD than those who had

taken less than 100 or greater than 400.

I want to close with what were the recommendations the committee, an ad hoc committee, of the National Kidney Foundation several years age: first, to avoid aspirin within 48 hours of a nonsteroidals in patients with contraction; second, discourage habitual consumption of acetaminophen; third, eliminate the over-the-counter analgesic mixtures; and, fourth, discourage prolonged usage of nonsteroidals.

There are a couple of things I have chosen to avoid. One is whether some nonsteroidals may be less nephrotoxic than other agents. There was a study a number of years ago in which Solondac had less nephrotoxicity.

I think in these studies, it's controversial. Nothing has clearly panned out. The pharmacologic basis for that may be unknown. It appears as though Solondac may not be in terms of drug problems with patient seen in the urine the way some other nonsteroidals are. I think that most nephrologists would probably avoid nonsteroidals regardless of which one they were in patients.

Secondly is the issue of COX-2. COX-2 is induced within the kidney. And the COX-2 knockout

mouse was important and necessary for normal renal development.

Those mice developed microcyst formations, developed feculae mirialii. And those clay mirialii which did develop, many of them were sclerosed. So I think that its ultimate goal in renal development would be interesting to see.

CHAIRMAN PETRI: Thank you.

We'll now open up the kidney for discussion.

(Laughter.)

MEMBER McCONNELL: It's sort of like after the best film award for the Titanic having been presented, they then come back with the best short documentary or something.

(Laughter.)

CHAIRMAN PETRI: Let me ask what I think should be an obvious question. There's no correlation within an individual patient with GI and renal toxicity of NSAIDs?

MEMBER McCONNELL: No, not that I'm aware of. You know, many of them, the necrotic syndrome is deemed as an idiosyncratic reaction. So I think it would be very hard to predict that those patients who had some sort of GI outcome, defined however you like,

would also have a renal outcome.

CHAIRMAN PETRI: Would that be true even in the endoscopic studies? The patients with more five-millimeter ulcers have no difference in their weight, sodium, potassium?

DR. LAINE: I don't know of any. And I don't think most people really look at it to be able to say, frankly.

CHAIRMAN PETRI: Dr. Abramson?

MEMBER ABRAMSON: I was just wondering your thoughts. I think it's important not to link this finding to COX-2 perhaps, despite the animals, because you have acetaminophen, phenacetin. And you have analgesic doses of NSAIDs.

So it seems to me we don't really understand the mechanism by which this chronic interstitial nephritis occurs. And it may not be related at all to cyclooxygenase.

MEMBER McCONNELL: I think that's true. In terms of the interstitial nephritis, that entity associated with necrotics, I don't think that's very true. In fact, we very often use nonsteroidals therapeutically purposely to decrease GFR; for example, those patients who might have massive proteinuria.

I think it's also important to recognize that aspirin appears to be quite beneficial in the pre-ischemia patient population.

I think with regard to why these may be involved in end-stage renal disease or papillary necrosis, the renal medulla is exquisitely sensitive to oxygen tension. And in those patients in which you reduce major area blood flow, you could very easily hypothesize because of that, you get ischemia, scarring, and the lack of comparative processes, leading to scar formation.

MEMBER ABRAMSON: Is there data, for example, that acetaminophen and phenacetin inhibit prostaglandins, particularly in the kidney? Because, to the best of my knowledge, they don't.

MEMBER McCONNELL: No. And, in fact, to the best of my knowledge, phenacetin is not greatly concentrated within the kidney. Acetaminophen, which is metabolized, is. And you can show within the kidney a gradient in the cortex medulla acetaminophen concentration.

CHAIRMAN PETRI: I wanted to welcome participation of the audience since we have the COX-2 world experts sitting in front of us. If some of the people in the audience would like to discuss COX-2 in

the kidney, if you could please come to the microphone?

MEMBER McCONNELL: I think, at least in abstract form, some COX-2 experimental agents have not been shown to decrease renal blood flow or GFR. I think others may do that more so. So, again, I think it's variable.

CHAIRMAN PETRI: Please identify yourself.

DR. ISAACSON: Peter Isaacson from Searle.

You made a comment about the distribution of the COX-2 in the rat kidney and also about the knockout mice. But I wondered if you'd comment about the paper that was in AJP last year from the German group, which really showed a very different sort of distribution of COX-1 and COX-2 in the kidney.

MEMBER McCONNELL: Yes. I think that, one, experimentally the rat and the mouse are very different in terms of, well, renal physiology. That is quite true.

In the mouse knockout data that you referred to, the distribution there was wider. It's also seen in potocytes and more generally throughout the areas where the rat seems to be more restrictive. Now, whether that will translate changing the function, we don't know.

DR. ISAACSON: For example, in the human, it doesn't seem to be expressed in the maculo densa; whereas, that's really where it's expressed very highly in the rodent.

Just one comment is that we see very high levels of COX-2 that are expressed in both the rat and the dog kidney after volume depletion, but in early studies in the primate, that doesn't seem to occur.

So I think we need to be cautious about extrapolating these animal studies to what might happen in people.

MEMBER McCONNELL: Did you look and see whether those adjust to the medulla or superficial cortical at all?

DR. ISAACSON: Well, you mean in the rat and the dog?

MEMBER McCONNELL: Yes.

DR. ISAACSON: Well, the distribution is pretty diffuse. I mean, it comes up in a lot of places, but the maculo densa, for example, all of them just explode in the dog and the rat in terms of COX-2 expression.

MEMBER McCONNELL: When? Volume?

DR. ISAACSON: Yes, when there's severe volume depletion but not again in the primate

apparently.

CHAIRMAN PETRI: Dr. Welton?

DR. WELTON: Thank you, Dr. Petri.

Dr. McConnell, that was both elegant and eloquent. And I would only add just a few morsels, so to speak, of additional window dressing.

I think the thing that comes across to me in recommendation to the Committee is that not only in looking at a database, an ISS for a new compound, would one want to review all of the syndromes that Dr. McConnell has reviewed, but I think it's important to keep striving to look for new entities also because my suspicion is we will see that in the future.

I was interested, as an example, when the question of the nephrotic syndrome was first described in the early 1980s and, as Dr. McConnell pointed out, usually designated in the literature as idiopathic in nature.

What struck me is that two-thirds of the worldwide reports come from one compound, phenoprofen calcium, which at the time of its peak use had a minority position in the marketplace, at least in the U.S., less than five percent. And that obviously gives us a message that if we were smart enough, we ought to be able to identify the mechanism.

My own suspicion is it probably has to do with an action on the leukotriene pathway, rather than on cyclooxygenase. And it's interesting to subsequently see that not only is minimal change glomerulonephritis a designated histopathology for the syndrome, but recently also the description of a membranous glomeruliopathy.

So I think, in addition to all of the things that Dr. McConnell has so effectively pointed out, I would suggest looking for new syndromes, taking the database of a newly developed compound, dredging through it carefully to make sure that all of the existing syndromes are carefully reviewed, and that there are no additional surprises.

CHAIRMAN PETRI: Dr. Welton, let me ask you to stay at the microphone because I'd like to address questions to both of you. The Committee, again, is charged with helping to design perfect studies. What kind of studies do the two of you want done to look at renal toxicity at the COX-selective NSAIDs? Could you tell us what realistically might be found in a study and what things you think are going to have to be put off to post-marketing?

Maybe I could start with Dr. Welton and then Dr. McConnell.

DR. WELTON: Issue Number 1, as Dr. McConnell pointed out, the most common side effect from the renal point of view will be the identification of edema, either peripheral characteristically or on occasion generalized.

Now, that fits in absolutely with the physiological role that COX-1 and, as we have heard, COX-2 play within the kidney. So this wouldn't be a surprise.

It's likely going to be manifest simply across the board in those who have a predisposition towards edema retention, such as incipient CHF, the elderly, et cetera. I think just looking across the database of a multitude of different designs of study will reveal whether that occurs or not.

CHAIRMAN PETRI: Andy, in like one month? I mean, how long would such a study be?

DR. WELTON: Under normal circumstances, this is an early onset event and will be seen within one to two weeks of the start of therapy. I cannot comment on the issue of absolute stability, but we know that this is a relatively early onset phenomenon, tends to be relatively stable.

There's usually a dose adjustment made in the drug or the concomitant diuretic administration.

I would agree with Dr. McConnell that looking at diuretic interaction with any new nonsteroidal is also an important issue, particularly with emphasis on the loop diuretics.

CHAIRMAN PETRI: Specifically chronic use of diuretics or addition of diuretic to someone who is on an NSAID?

DR. WELTON: It would be a drug-drug interaction phenomenon because loop diuretics depend almost 50 percent on their functional manifestation by the mechanism of stimulation of prostaglandin production within the inner zones of the kidney. So there is a drug-drug interaction that will blunt the effect of the diuretic.

Next issue in thinking about study design that comes to my mind would be the question of acute deterioration of renal function. Now, it is in that setting that I would suggest to the Committee that special populations be identified, as Dr. McConnell pointed out, those with preexisting chronic renal impairment.

We know from most available data that in a stable chronic renal failure population, a creatinine usually in the range of two milligrams per deciliter or higher as a very simple rule of thumb

puts such individuals at risk. So I think the stable population of chronic renal failure would be desirable.

CHAIRMAN PETRI: And how long would you want to study that special population?

DR. WELTON: Onset if it's going to occur is characteristically within five to ten days. So it's, again, a fairly rapid onset phenomenon if it is going to occur in any individual with stable preexisting chronic renal failure.

As an additional study population along these lines, I would also suggest that the elderly be considered because, as Dr. McConnell pointed out, they are a separate at-risk group.

As a consequence of the aging process by age 80, approximately 50 percent of the general population in the U.S. will manifest 50 percent reduction of glomerular filtration rates.

So it is in that age range, the octogenarian and upwards, where I believe that age becomes a specific independent factor. And I believe that that should be assessed as a special population.

CHAIRMAN PETRI: Let me quiz you about tubulointerstitial disease and nephrotic syndrome.

DR. WELTON: Yes.

CHAIRMAN PETRI: That's going to be very rare.

DR. WELTON: That's right.

CHAIRMAN PETRI: But would a renal biopsy study pick up patients who are subclinical?

DR. WELTON: No. I think that this is going to be entirely a post-marketing surveillance study. It was quite some time with availability of nonsteroidals before the syndrome was identified. The drug that has the highest profile is not used to any great extent any more.

So I think that this is purely an issue for post-marketing surveillance, as is the question, in large part, of both acute papillary necrosis, which is distinct from the chronic papillary necrosis that Dr. McConnell pointed out. These will be post-marketing issues.

MEMBER McCONNELL: It might be hard also to biopsy someone. You have to be absolutely sort of knitting every bleeding problem.

CHAIRMAN PETRI: Let me ask both of you: As a special population, do you want to study patients who have stable nephrotic syndrome?

DR. WELTON: They are at risk to the development of acute renal impairment as a consequence

of their low oncotic concentration or low oncotic activity intravascularly, causing vascular contraction and, ergo, reduced renal profusion. So as a group, they simply will be at risk for acute deterioration of renal function.

I would not think about studying them as a separate group for any other reason than that.

MEMBER McCONNELL: Are you thinking about from the standpoint of side effects or benefit? There may be a benefit. I mean, you're not going to -- let me see if I understand your question correctly.

People with nephrotic syndrome are not going to be more disposed to develop this interstitial nephritis. You shouldn't see worsening. You were thinking from the standpoint of whether they might benefit.

CHAIRMAN PETRI: Well, in our rheumatology field, there are several studies that suggest that NSAIDs might reduce nephrotic syndrome.

MEMBER McCONNELL: Well, I think by reducing GFR, you do see a reduction. Now, suppose a study -- I'd be interested in your opinion -- in the diabetic, for example, who has a small amount of insipid diabetic necropathy who has got albumen excretion rates that are abnormal and whether those

patients might be interesting to study from the standpoint of being able to reduce their albumen excretion rates to see whether you get an amelioration of disease or changing the time course.

Secondly, there is some data that patients who are at risk in the future for cardiovascular events you can define early on by having abnormal urine albumen excretion rates. And, again, they might be an interesting population to study from the standpoint of benefits.

I mentioned the diabetic because in that population, if you graph one over creatinine over time, we think they have a fairly straight-line decline in their renal function so that each patient may be able to serve as its historical control by seeing what their decline is over time starting with the COX-2 agent and then seeing if there's some deflection in that curve.

CHAIRMAN PETRI: Let me ask both of you about another special population: the stable hypertensive on different drugs. Is that also something that should be studied?

DR. WELTON: Yes, I believe that it is. I think that's another special population that deserves consideration. The available data would

indicate that there is a sufficient change in both systolic and diastolic blood pressure in treated hypertensives, particularly those who may not be very adequately controlled in terms of blood pressure.

An intercurrent use of a nonsteroidal, at least the available family of nonsteroidals, can tilt the pressure upwards by a range of three to six millimeters, both systolic and diastolic.

CHAIRMAN PETRI: Is that always explained by fluid retention or are there other mechanisms?

DR. WELTON: There are probably at least twofold mechanisms. One would be the issue you have identified: fluid retention. And the other may relate to the mechanism by which the drug expresses its anti-hypertensive effect, most notably with the converting enzyme inhibitors. That may be an issue in terms of the mechanism.

In normotensives, the effect in blood pressure is sufficiently minimal that it probably is not a major issue and would only be identified by using ambulatory blood pressure monitoring.

I would think in the treative hypertensives' ambulatory monitoring is probably also the most useful way of identifying these small changes in systolic and diastolic.

CHAIRMAN PETRI: Let me ask both of you if there are any other special populations that we have not mentioned. Dr. Simon?

MEMBER SIMON: Well, Andy or our guest, could you explain whether or not we should look at patients with clinically and hemodynamically significant congestive heart failure?

Should it be required to look at patients with clinically significant but ambulatory liver disease, patients who are at risk for significant dehydration? Are these patients who should be studied?

And if these drugs are going to be considered for peri-operative states, should we look at patients who are potentially dehydrated or postoperative under those circumstances?

DR. WELTON: Well, that's a very important issue. It all, Dr. Simon, falls under the rubric of preexisting reduced renal impairment. And the chronic heart failure, severe liver disease, protracted dehydration occurring in an individual who may at baseline have normal renal function but gets a chronic diarrheal illness or something like that may all fit into the risk category for the induction of acute renal failure.

So it seems to me not as important to identify those with preexisting liver disease or incipient heart failure or known heart failure, I should say, as a separate population for study. It may be a desirable issue subsequently, but I --

MEMBER SIMON: Michelle, can I expand that one more second?

CHAIRMAN PETRI: Of course.

MEMBER SIMON: There is some evidence in the pediatric literature that kids who get dehydrated for any number of different reasons are particularly at great risk for presently available nonsteroidals to induce kidney failure.

And I'm a little concerned something about pediatric rule and some issues about the assumption that certain drugs are okay for kids if they're okay in adults, particularly if they're not studied very extensively, particularly in subpopulations of kids.

Are there reports about kids who drink alcohol, who get into trouble with taking nonsteroidals? There are some reports about adults who drink alcohol and get into trouble with kidney failure related to nonsteroidals. Could you comment on that particular issue?

DR. WELTON: Yes. There are those

reports, and it's reported to occur with relatively large intake over a short period of time, such as 24 hours, leading to the development of acute renal failure.

Likewise, as you sure are well-aware, this has been reported in otherwise healthy marathon runners, who at the end of a race being dehydrated having a tendency to rabdumyelosis, just a singular administration of something as otherwise innocuous as ibuprofen, relatively high-dose, will produce profound acute renal failure.

So I think those were all special circumstances. And it's to my mind difficult to produce a mandated study for those kinds of settings. Again, I think that will be in large part post-marketing surveillance.

CHAIRMAN PETRI: Other questions from the Committee?

(No response.)

CHAIRMAN PETRI: I'll let Dr. Welton rest. Thank you.

Are there other comments from the audience? Yes, Dr. Ehrlich?

DR. EHRLICH: Thank you, Madam Chairman.

I've been listening here very intently

because of some of these arguments, of course, and some of these discussions we had in the years past when I was on the other side of the table. And I've never really come to grips with some questions.

One of them is, of course, that NSAIDs, including aspirin, have been around for a very long time, long before we knew about the prostaglandins and in recent years long before we knew about the two COX enzymes. And it's possible that in future years we're going to find some other things that some of them work on to explain some of the quandary.

The second thing is that we obviously as a community of physicians think of NSAIDs as relatively safe because they're widely used. We've in years past permitted several to go over the counter. And they're widely used.

So there are millions of people taking them. And, even if there's a slight drop-off in the amount of NSAID usage for a variety of reasons, they still are amongst the most prescribed or most bought medications.

A small proportion of patients clearly do have complications. Now, we heard this morning in these excellent presentations that the biggest risk is early. And so obviously, as part of their action,

they can cause some of these over-actions, which we identify as severe risks. And these are acute.

On the chronic ones, we have more problems. And the reason we have problems is that then we come into background noise, and it's hard to know whether the manifestation is because of other factors in the background or whether it's because of the medication that's been taken for a period of time.

We're not always sure of that. In particular, if we make it mandatory to diagnose a complication of an intervention, then the intervention is necessary. And that creates a certain amount of circular reasoning.

We do see some of these things that you have described in people who do not, to our knowledge, take NSAIDs. We do see some of the things that Dr. Laine told us about so eloquently in people who don't take NSAIDs as well.

And then Dr. Laine reminded us that some people, despite the continuation of taking these drugs, do reasonably well and lose some of these manifestations, at least the less serious ones, which leads to the question: If we weren't monitoring, would we know about some of these things?

And it raises again what I once commented

from your chair, that, as duBois has pointed out, the measurable drives out the important. I want to emphasize that we should look for the important. And we need to find measurements to identify the population that's likely to be at risk.

We're not going to abandon these compounds. We're going to look for safe versions of these compounds to be sure. And it's one of the reasons that you're having these meetings, to find out how to find safer versions of compounds that will antagonize inflammation and relieve pain because that's what we're after.

But in the process, we need also to keep in mind that we as rheumatologists and the family physicians are the ones prescribing these compounds. And the problems are funneled to the gastroenterologists and the renalologists who clearly see these drugs as problematic because they see the problems.

But generally in the office practice, one sees these relatively rarely or, else, they wouldn't be being prescribed to the extent that they are and they wouldn't be on the shelves of our supermarkets for people to pick them up ad lib when they identify their own problems.

CHAIRMAN PETRI: Thank you. Let me ask our FDA representatives if there are other specific points about special populations or study design they wanted to bring up at this time.

(No response.)

CHAIRMAN PETRI: Well, I want to thank Dr. McConnell.

I think this might be a good time to take a 15-minute break.

(Whereupon, the foregoing matter went off the record at 10:39 a.m. and went back on the record at 10:59 a.m.)

CHAIRMAN PETRI: Our charge between now and lunch is to begin the discussion. This will eventually be pointed to the questions but I wanted to start by asking each committee member to voice their concerns or their major take-home message from this morning's discussion to this point.

I'd like to let everyone participate in this so I'm going to go around the table. So if I could start with Dr. Fernandez-Madrid?

DR. FERNANDEZ-MADRID: Thanks a lot. Well, I think the -- as I see the questions, what constitutes the type of equation and what control studies which would be clinically meaningful, I don't

pretend to educate the group on how to do its study. I think we have gone through these.

I would talk about a couple of things that were suggested to me by this morning's session. And one is that we have talked mainly about adverse effect of -- potential adverse effect of newcomers to the field, COX-2 inhibitors, and how to design a study.

And I think these questions seems to me bypasses the question of efficacy that we assume -- or the hypothesis assume -- that the efficacy of these new drugs doesn't have to be looked at because all the frequency of the non-steroidals that are known is equivalent.

And I don't think that I assumed this -- that is, I assumed that these will be new drugs. And I believe that these data suggesting that COX-1, it involves also an inflammation, and we may lose something of efficacy when we look at a very selective COX-2 inhibitor -- a very specific COX-2 inhibitor.

So I'm ready to look at efficacy as well as adverse effects of these new drugs.

The GI section was very illuminating and I think it was clear to me that the semantics are important; that is, preventing injury doesn't seem to me equivalent to preventing ulcer. And it seems to me

that we have to review how much endoscopy we will advise and it seems to me that from the past we have done probably too much endoscopy in these studies.

So one would like perhaps, to do a baseline endoscopy, but I don't think that we have to do endoscopies every month or every now and then in symptomatic patients. I think we have to look at major events and the incidence of major events.

I think there are a couple of other things. In reference to the renal, I think we were told that we know that many of the non-steroidals have gone OTC. And I was tickled by the conclusions -- some of the conclusions of Dr. McConnell.

I think one was, OTC -- what was the conclusion -- eliminate mixtures, analgesic mixtures. And I submit that patients make these analgesic mixtures. We prescribed a new, non-steroidal that the patients take OTC analgesic and make these mixtures.

And in terms to populations at risk, I had at least two patients with rheumatoid arthritis, not elderly, that were treated with methotrexate, which is a very safe drug, and were not instructed to take non-steroidals but they were taking one of these mixtures, including non-steroidals.

And these patients developed transient

renal failure. And I think the transient renal failure has a connotation of being a benign problem, but it's not a benign problem. It may be a malignant problem because the clearance of a drug like methotrexate can be severely decreased in a patient taking non-steroidals.

And these two patients that I'm talking about, died with infections secondary to bone marrow suppression, which is unheard of in methotrexate treatment.

So in terms of potential populations of patients to be looked at, I think the populations of patients with chronic disease, with rheumatoid arthritis, with a variety of other problems that rheumatologists treat, should be looked at.

CHAIRMAN PETRI: Thank you. Dr. Callahan?

DR. CALLAHAN: Initially, my first comment is, I think one thing I derived, there are a lot of complexities to this. I think there will be certain risk factors that are clear and have been shown in a number of studies that would be taken into consideration throughout; such things as age and the steroid use.

The other thing that came through clearly is that there's a lack of knowledge on the clear

predictors with the important clinical outcomes, and that some of the issues in determining those might be best determined later in post-marketing surveillance or in terms of the power issues; that some of the size of samples to answer certain questions we kept asking, just may not be determined.

And the other is that there are clearly a number of compounders that are going to have to be looked at in this study.

CHAIRMAN PETRI: Thank you. Dr. Brandt?

DR. BRANDT: And one can't help but be struck by the number and the size of the gaps in knowledge that confront this issue.

I'd certainly agree with Dr. Madrid's comments with regard to issues of efficacy and are these agents comparable to existing NSAIDs with regard to efficacy? Are there new side effects that we're going to see with those beyond differences with respect to existing side effects?

I think one patient population that perhaps we didn't mention that may be worth considering -- that is worth considering -- are people on anti-coagulants. The point about getting data on the elderly is very well-taken, particularly with regard to the growing problems of osteoarthritis in

this country.

In that respect, there's a lingering question which existing literature has not contributed very much to, and that is the question of whether non-steroidal, anti-inflammatory drugs are good or bad for osteoarthritis -- not with regard to symptoms but with regard to disease progression.

And I submit there are no good data at this point to answer that question in humans. There are some studies but they have problems. One of the limitations that has existed with regard to attempting to answer that question in animal models -- given the limitations of transferring animal models to humans -- has been the very striking GI sensitivity with all the existing animal models to NSAIDs -- whether it's the dog or the guinea pig or the rabbit or the mouse.

They all have the problems that I think, Dr. Laine alluded to. They all died before they developed their osteoarthritis -- whether treated with NSAIDs -- of hemorrhage and perforation. These selective agents may provide an opportunity to look at whether in fact, the NSAIDs used in higher doses than we can then use today, may in fact, be in fact be disease modified or not.

So there's an opportunity there at a pre-

clinical level initially certainly, that perhaps shouldn't be overlooked.

CHAIRMAN PETRI: Thank you. Dr. Simon?

DR. SIMON: Many of the comments this morning really resonated with me about some of the issues about non-steroidals as we think about them today: the policy of class labeling of non-steroidals when we have excellent evidence regarding certain effects of certain drugs versus certain effects of other drugs.

And now that we're confronted with the potential for the consideration of drugs which some people would claim are non-steroidal, anti-inflammatory drugs with a unique flavor, or that they are in fact, a different class of drugs with different effects and different expectations.

I think that the comments that Dr. Weintraub made before about the idea of thinking about the evidence that's out there in the literature and as we understand it, and then labeling this particular series of drugs in that manner, makes a lot of sense to me.

I'm a little concerned about some of the information that is being kicked around, both in the literature and in publications that are not peer

reviewed, and in speeches, that are related to the issue of anti-inflammatory activity of drugs and what the mode of action is -- particularly as efficacy.

As Dr. Madrid said before, the concept of COX-1 being important in driving inflammation versus the importance of COX-2, the relative flavor of inhibition of both, I'd like to hear a discussion about that. We have experts in the audience as well around the table, that can reflect on the importance of inhibition of COX-1 as it relates to progressive inflammation.

I'm not entirely sure that we understand how much importance there is, and I'm not sure there's a lot of evidence that supports COX-1 as very important in driving inflammation. I think that has serious ramifications about how we think about these drugs as potentially a new class or not.

I think that the side effect issues are really critical. I've been interested in some of the effects of non-steroidals from a toxicity point of view, and have been confronted consistently by people asking questions about the issue of endoscopy and what it means as it relates to outcomes.

I think that endoscopy tells us a lot about what we can predict, although not on a by-

patient basis. I think the importance of endoscopy is it allows us to understand in a more efficient, cost effective manner, perhaps a surrogate, perhaps not as good as we'd like, that what could be a potentially good or better outcome.

I mean, if you have an ulcer that sits there with a pulsating artery sitting in its crater, that's probably not a good thing, and if you can decrease the incidence of those probably not good things, you probably have a better outcome.

And I think it's easier to see that then it is to spend $10 million on 10,000 patients for 12 months. Although I don't think we should not do that; I think that's also very important.

I'm also troubled by some of the issues regarding the kidney, and I'm troubled by those as they relate to some of the other, more obscure effects of these drugs, particularly as it relates to bone, perhaps ovarian function, perhaps brain function -- that have been claimed to have been not distinctly reported in the literature.

And I'm also concerned about the use of these drugs in children potentially, without really having adequate studies to help us understand better some of those effects. And I think we have an

opportunity to correct some of the problems that were raised by the studies using -- in studying non-traditional steroidals, and perhaps we can correct some of those outcomes as we look at this new series of drugs so we can understand better how they really effect people.

CHAIRMAN PETRI: Thank you. Dr. Liang?

DR. LIANG: I think it's all very interesting and potentially very useful in terms of increasing our understanding of basic mechanisms and possibly a major therapeutic advance. History tells us I think, that for every medical advance there's an equal and opposite effect -- especially from a point of population health.

And I don't think we can sit here in a room and guess what will happen when the rubber meets the road and it's used more widely. And by definition, rare and chronic adverse events you can't study until you either have the cumulative experience or the cumulative time of observation.

And I think from a societal point of view we do that the worst. I mean, we spend a lot of time putting up hurdles for industry to get drugs to market and then we just sort of up and go. I don't ever see good surveillance studies -- or at least, they could

be vastly improved.

So I'm one that would, you know, try to, in terms of indications, make people define them very narrowly and also be fair in telling the consumer -- potential consumers -- how long we've studied the agents in terms of duration. And then as good data becomes available, to expand those indications, rather than to try to front-load and make the indications too broad.

I'm also wary of predictions based on what we know now because everything -- predictions are frequently caricatures of the present. And so the things that we do now for COX-1/COX-2 inhibitors in terms of what we've learned about measuring their efficacy as well as their toxicity, I think we should not assume that those are going to be operative with new agents.

And we should bend over backwards to, in these early trials, develop metrics that will capture things that we know about and possibly things that we don't know about; but to actively look at them with vigorous methodologies. Like the mucosa trial, I think it's almost more important that we have, you know, other specialties represented that may be affected by COX-2 inhibition.

CHAIRMAN PETRI: Thank you. Dr. Abramson?

DR. ABRAMSON: Well, I mean, I share some of what's been said, particularly the excitement of this whole field and what it's taught us about disease and physiology.

I'm disappointed -- I just had my slide made up with a new paradigm and Dr. Palmer informs me I have to change my slide on a new hypothesis. I've got to go with my housekeeping genes and my pathological genes. But I think we're always learning. I think that's real important.

My hope is, is that you know, although these are a new class of drugs, the COX-2 inhibitors are different chemically to some extent, so therefore we have to be vigilant looking for new toxicities.

To the extent that we've been able to inhibit across the gland that's in this tissues with our non-selective drug, I'm a bit sanguine that we won't find any unanticipated outcomes that consequent -- that result, that is, from inhibiting across the gland. At least one -- I'm hopeful in that regard.

But I guess the purpose of today for all of us is to figure out how to judge this at the clinical level because that ultimately, despite the science, becomes the charge now. And obviously there

are several areas that need to get sorted out.

In the clinical studies, the one being the GI toxicity, and relative usefulness or value of endoscopies that are built-in in routine ways that may in fact, give you information you don't know how to interpret, and may in fact, cause you to exclude patients who have significant ulcers who might never get clinically-relevant ulcers.

So I think a major -- or for this discussion we'll decide whether after three months certainly, one needs to do regular endoscopies or just have clinical indicators upon which endoscopies would be warranted. So that's a big issue.

The other issue obviously, is choosing patients that we study their risks for side effects with any of these drugs. That is not to exclude our patients. How do we be sure that people who are on other medications, the aged population, are fairly evaluated in prospective clinical studies? Because there are predictable outcomes that may not be seen in a more restricted kind of clinical study; that we need to be wary of.

And I guess the third issue which we have -- which got touched on a bit -- we talked about GI toxicity and renal toxicity. We haven't really sorted

out a related issue -- which may not be important, ultimately -- which is whether a drug is really a COX-2 inhibitor that's selected for preferential, and whether that matters at all with regard to the clinical outcome studies that we're discussing.

So those are several issues that I picked up from this morning.

CHAIRMAN PETRI: Dr. Yocum?

DR. YOCUM: Well, we do a lot of studies and I guess in listening today I was impressed that in such a well-studied field how little we know in actuality.

Having done a lot of studies, I often think we're studying the wrong population. I worry that we don't actually study the high-risk patients that Steve just brought up. I think especially the aged. They are often eliminated from studies or can't get in because of their problems, but often are exposed to those drugs.

Patients with concomitant illnesses because of exclusionary items in studies are eliminated but will get these drugs once they're released. And I'm concerned about combination therapies and commented earlier on. The data on aspirin is very worrisome to me because basically when

you see the data, more and more people are taking this for strokes, cardiac situations.

Also OTC drugs -- how potent will the kind of selective agents will they be? Will patients who have the greatest amount of pain be doing more over-the-counter medications? We have to worry about that. Agents such as Cyclosporine which are gaining in use, what will the combination of those agents on the kidney be?

As far as endoscopy studies go, I must say having done many of these I'm a bit unenamored with these because I think the patients that did endoscopies are not the representative patients. They're often patients of medical students, the patients who need many, and the high risk patients often don't get it.

So it may actually be worse than we think and there be more predictive value if we could get patients who are high risk to do things.

So I think we're either facing limited labeling earlier with long-term studies to demonstrate safety as has been pointed out, for making the hurdles higher and expecting more studies to get more broad-range labeling.

So I think there are a lot of issues to

face, and I go back to the other day. One of our Fellows came up and was presenting a patient who had diarrhea and then he said well, there's a drug here I just don't know about. He said, it's meclofenamate. What is that?

And it's amazing in the HMO world how old drugs now are coming back, because they can market for these. But it's kind of interesting; if this drug came out and was produced again, what would be the use again? I don't know.

CHAIRMAN PETRI: Thank you. Dr. Katona?

DR. KATONA: Looking from a pediatrician's point of view I'm really excited since we in Pediatrics, think of NSAIDs as the drug -- a drug's power to usage is the longer time used and possibly the safest for the children.

So to think about the possibility that there will be a new class of drug with similar effects is very exciting for us.

Dr. Simon very eloquently talked about some of the problems we have been encountering in Pediatrics and the additional things what I just would like to bring everybody's attention which is not as well known, that children who have this panacea, they don't have ulcers, they bleed, and they perforate.

Not with the frequency as older adults but we still see every day in our clinical practice, those problems.

And overall I am very excited about -- I've learned of the complexities today and I think it's very important to me that COX-2 has important physiologic roles.

And in addition to I think, what everybody has discussed in detail, I just would like to add that the developmental issues -- effect on bone maturation as well as reproductive issues -- are very important for us in Pediatrics. So those would be the areas where I would like to see specifically addressed.

And one additional thought. Pediatrics' problem is drug clearance. You know, we all know that kids have good kidneys, good liver and by-and-large, there are a lot of drugs which have a much faster clearance, especially on the little ones than on adults. So really figure out the appropriate dosing is going to be very important if you use it for children.

CHAIRMAN PETRI: Thank you. Dr. Harris?

DR. HARRIS: Thank you. This was, you know, a very interesting morning. I actually raise the following points. What is the central usefulness

of these COX-2 inhibitors? And then the second point of all this is that we have presumably found an agent that is more efficacious; that is, less toxic. And then presumably, toxicity to the GI track, which is the main toxicity identified by non-steroidal agents.

If one is going to demonstrate that, I think that it is critical that one shows, of course both efficacy, and with respect to toxicity, that it's toxicity which is clinically relevant.

And I think this morning there was enough discussion as to the clinical relevance of endoscopic studies. Obviously, we used it all along as a surrogate for clinically-significant studies. I don't know if we should hold new drugs to new standards and call for clinically-relevant or to more clinically-significant side effects.

But certainly from the point of view of the practicing rheumatologist, it is important to us to understand what toxicities exists that are going to be important to our patients. And that is bleeding ulcerations and perforations. So any study, I feel and claim, must at least get at that.

There's a second point I want to make, and as a rheumatologist I feel relatively comfortable with many of the non-steroidals, but where I am

uncomfortable is with special populations. It's patients with history of peptic ulcer disease, patients who have -- are in cardiac failure, renal impairment -- they're on anti-coagulant drugs and so on.

It is in these particular populations that I think we have so few answers. And I feel if there are claims that are legitimate claims which are going to be made, that these new class of agents -- or one at least would like to see that special populations are considered in some way. Certainly, at least, the elderly.

One may argue whether or not patients with a history of peptic ulcer disease -- but you know there is possibly ways of designing studies with respect to that. But I think it's an opportunity too, for the people who make these agents, because there is no problem or difficulty I think, as a rheumatologist, prescribing non-steroidals right now, then in fact, trying to assess which agent to use in these patients who are at particular risk of GI toxicities and renal failure.

CHAIRMAN PETRI: Thank you. Ms. Malone?

MS. MALONE: As a representative of the consumer and as a rheumatoid arthritis patient for 30

years, I was particularly excited about this because I thought, well at last there's something new. I'm disappointed because we've talked more about the toxicity, the risks. We haven't said enough about how good are these drugs? Now, are they that much better than NSAIDs? And I'd like to hear some more about that.

We do have to always weigh the risks against the efficacy. If a drug doesn't do any good you're not going to take it. Okay? I mean, that's a given. The consumer today it's a lot more educated about the risks. They do read; they have opinions.

But I think much of this goes back to the individual rheumatologist and what they know about the drug and what they're going to say to the patients. Many of the patients will take the word of the rheumatologist. And we have to be sure that the studies, you know, get back to them so that they know what the drugs are doing and what they can potentially cause.

One of the problems that Dr. Fernandez-Madrid brought up is the mixture of various drugs that people are taking. And several of the other doctors have brought this up too. And it seems as the population ages we get more and more special

populations that we're trying to target or not target. But more and people are falling into these groups. Okay?

I'm over 50, I have arthritis, I've had a heart attack, I take an anti-coagulant. So does that mean nobody can test me or nobody can do anything for me? So I think, you know, you never get this clear-cut, pure patient to deal with. And to design all special populations -- I mean, we're all special, but we're all, you know, a mixture.

And the truth is that these drugs are going to come out -- they may have been tested on special populations but the average patient, you know, with all these concomitant things wrong with them is also going to be using this.

So there needs to be a lot of clearness I think, when you're writing about what the risks are, without demeaning or negating the efficacy, you know, that this drug can do some things. And these are valid risks. So that the patient and the doctor can together, intelligently weigh whether or not it's worth the risk.

CHAIRMAN PETRI: Thank you. Dr. Moreland?

DR. MORELAND: Well, I can't follow up to do anything better than what was just said, but in

coming at the rear-end here of these comments I would agree with everything but I would like to echo two things.

One, I think our task is to decide whether endoscopy studies are needed. And two is, I would echo the comments that have been just made. We need to put into these trials the real patients -- those patients who need to be taking aspirin, those patients who are on anti-hypertensives -- and not take the medical students and examine them too much.

So I think we need to come back and look at the real world and underlying patients.

CHAIRMAN PETRI: Thank you. Dr. Pucino?

DR. PUCINO: Yes, I express the same concerns. After listening to our eloquent speakers from this morning and reviewing the material, there are at least nine confounders for doing toxicity studies, and so all of these need to be taken into account as well as numerous others.

So that we're left with two options. One is to use extremely large, multi-center trials, or to study the high risk populations. And as a pharmacologist I'm also interested in the drug interactions, particularly things like water and diuretics; that the trexate, glucocorticoids and other

drugs such as anti-platelet agents.

And finally I'm interested in the pharmacokinetics in some of these special populations -- geriatric patients. We know very little about the free drug concentration and elimination and the half-lives and they're doubled with these type of agents, and also renally eliminated metabolites where they're active, whether they accumulate, whether they convert over back to parent compounds.

CHAIRMAN PETRI: Thank you. Now, as I look at the questions I can see an easy division. The first question is asking us about efficacy; the second set of questions are asking us about GI toxicity; and the third is a grab-bag of other potential toxicities: renal, but then also bone and reproductive toxicity.

So I thought it would be best for us to start with the efficacy question. Dr. Fernandez-Madrid pointed out that we ignored that so far this morning. So let's come back to the thing that I think is going to be the greatest interest to our patients; is how are we going to show that these drugs work and are they better than what's currently available?

I think everyone on the committee needs to be reviewed about what the current standards or guidelines are for a study; of a need to NSAID in

terms of efficacy. So if I could ask either Dr. Hyde or Dr. Witter, or even Dr. Weintraub to review with us the standard guidelines?

DR. HYDE: Well, you're I think, aware of the guidelines for RA studies that have gone through this committee and are nearing finalization. And the OA is here also, where we're beginning work on that, too.

Basically, I mean it's two adequate and well-controlled studies is the mandate for efficacy. And that would apply to the separate indications of OA, and separately to RA.

CHAIRMAN PETRI: So right now it would be two studies for OA and two studies for RA as well?

DR. HYDE: Right.

CHAIRMAN PETRI: And is there a recommendation on the length of time of an efficacy study for an NSAID?

DR. HYDE: As far as efficacy, in the RA guidelines now it's three months. For OA we're still, you know, sort of working on that. I think, you know, historically about six weeks is what's been typical.

CHAIRMAN PETRI: In the general population?

DR. HYDE: Yes.

CHAIRMAN PETRI: And how long is it for the general population for an efficacy study for an NSAID?

DR. HYDE: What do you mean, in the general population?

CHAIRMAN PETRI: To show efficacy of an NSAID in the general population, what is the current recommendation for the duration of the two, well-controlled studies?

DR. HYDE: Okay, well, I mean, as I said they're separate for RA and not for OA. The --

CHAIRMAN PETRI: You told us three months --

DR. HYDE: -- safety follow-up, is that what you mean?

CHAIRMAN PETRI: No, efficacy. Pain, headache, whatever.

DR. HYDE: Yes, we're recommending -- that's three months for RA indication and I guess we're targeting, sort of six weeks for an OA.

CHAIRMAN PETRI: Okay. If I could ask for just general comments from the committee, and of course I'm very interested in comments from the audience as well about efficacy. Perhaps we could start with Dr. Simon.

DR. SIMON: Let me just be clear about the question you're asking. Are we talking about --

CHAIRMAN PETRI: The first question. Why don't I go ahead and read it so we're all starting at the same place.

The first question is : What constitutes the type of adequate and well-controlled studies which will be clinically meaningful?

DR. SIMON: Okay. It seems that we had a large library of studies that have been done to-date using traditional non-steroidals, looking at OA and RA, that have looked at various different effects -- efficacy-wise -- of various drugs compared to placebo, compared to other drugs.

And usually the other drugs are chosen based on the marketing issues of how often they're used and the community they're used in.

And sometimes the dosages are a little surprising that are chosen from the active comparators, almost as if -- far be it from me being the accusatory -- almost as if somebody's trying to show that a particularly okay drug may look a little bit better than it really could be if you're using an active comparator at a relatively low dose.

So I think that we need to be very clear

that the drugs that are going to be active comparators -- which I think it's very important to have active comparators -- have to be chosen at a dosage that are going to be predictably efficacious.

And so therefore we can get useful information about these new drugs as to whether or not they're equally efficacious or more efficacious. And we have to be very consistent. The RA guidelines define specific outcomes that have to be measured, and we have to remember to include the assessments that are associated with the identified ACR responder indices and whatever.

At the same time we have to remember how those were designed and defined, which were more for drugs that actually alter disease processes rather than drugs that are just supposedly, putatively analgesic and anti-inflammatory.

I think the other issue is that quality of life measures are really critical in measuring these qualitative outcomes, and I think that we have to remember that although we don't yet have a guidance document from the FDA in OA, we have to be realistic about what can be measurable and what things are implied by the measurements that we presently have as relates to the outcomes that we can determine.

And it would lovely to have structural outcomes; we don't know what they are yet. So therefore, I think we need to clearly identify that we need to know active comparator comparisons, we have to look at the broad range of response -- be it biologic measures as well as quality of life measures -- and we have to have adequate patient populations to determine the real outcomes.

CHAIRMAN PETRI: Let me pin you down. Just one active comparator?

DR. SIMON: No, I actually -- if we're looking at a potential class of drugs that are perhaps to claim that they are superior in efficacy, I think the only way they can -- that can be claimed is that in fact, we have a broad panel.

And I think it can be pretty easily defined partially by the marketing issue of how many -- what types of non-steroidals are classically used in the United States and when they're applied in various, different diseases.

I think in RA that's easier. I think in OA one might have to consider for a superiority claim, a comparator towards acetaminophen as an analgesic. And I think that's going to be very difficult.

I'm also a little concerned about active

comparators as it relates -- and I know this is not exactly the topic related to toxicity, but we have to remember, if we're going to take high-risk patient populations for a potential GI outcome, study that patient population as an active comparator for efficacy, and have within it, built-in a safety assessment, then how are we going to ensure that that patient population is afforded the state-of-the-art therapy to prevent a bad outcome when given an active comparator that we know may induce an ulcer?

That will then stack the deck against the real assessment of the bad or not-bad outcomes associated with this new study drug, because if we're going to prevent the bad outcome by a prophylactic agent -- which would be required based on state-of-the-art therapy -- then we're going to have a difficult problem in ascertaining outcomes.

So we have to be very careful about the kinds of implications that will be required based on some of the questions we're going to be asking.

CHAIRMAN PETRI: You mentioned active comparators chosen on the basis of marketing or the particular usage in that disease. What about the active comparators in terms of their mechanism of action?

Do we want to have a COX-1 directed -- a mixture COX-1 and COX-2 and then a COX-2 selective?

DR. SIMON: You're talking to the wrong guy. I actually -- I don't see this whole argument, and I'd like a discussion about this issue of mixtures of predominant COX-1, minimal COX-2. And I think Steve raised the issue before about selective preferential.

I think that we are looking at drugs, looking at some of the basic biologic effects that really do, in efficacious therapeutic dosages, seem to have a different effect on those ratios, or on those issues, than do the presently available, non-steroidals.

I am unconvinced by the large, patient population studies that there are dramatic differences that are in fact, really measurable when really comparing drugs at equal efficacious, therapeutic dosages.

Since I've already defined my active comparator as being used at an efficacious, therapeutic dose that would be justifiable, therefore, I would expect that there would not be great differences among those drugs -- whatever comparator you chose.

I do think that there's some evidence that people have claimed -- and many of these large population studies have chosen -- to use Ibuprofen™ at relatively low dose, making it seem very safe. The recent Henry meta-analysis demonstrated that when you use it at a higher dose it's no safer than any of the other non-steroidals.

So therefore, I would not demand that we would select a more COX-1 selective drug and then a mixture of drugs. I would actually select them based on their usage. We are clinicians. We know which drugs are kind of popular in their application to patients, and I would be interested to see how they act in relation to this new class of drugs, because we believe these work. That's why we used them.

CHAIRMAN PETRI: Let me open this discussion up to other members. Dr. Yocum?

DR. YOCUM: I share a lot of Lee's comments, especially as far as relevant dosing. And what's in the studies, we often see that agents are approved at what's I think, is a borderline between toxicity, efficacy, and then when it gets into the clinical setting it starts on double the dosage if we follow the agents.

So that I think two doses of the drug

should be included in taking the targeted dose for the sponsor and then looking at some dosage elevated above that to look at what's going on.

I'm constantly concerned about placebo-controlled trials. As I say with my IRB I can picture keratine labeled as a biologic these days, but if I come forward with a new, non-steroidal or COX-2, I suddenly find myself before my IRB, commenting on why I'm developing a new drug. So many of these are already available.

And there are always concerns about the placebo, not as much in the OA, but clearly in the RA patient because they're concerned about pain and suffering. Also worried about who entered the placebo-controlled trial. Are those really the worst patients that we're looking at, or in fact, do you kind of pre-stack the deck with who's willing, you know, to come in to a placebo-controlled trial?

So that I think in a way, I don't have any problems with going to a more Tylenol™ comparator than a placebo comparator. What should be the comparator in RA? Maybe it should be the non-steroidal du jour. I don't know; whatever they're using to look at that to get an active comparator for RA.

Duration of the study, I think everybody's been excited and we've seen on TV recently the placebo response and how long that that can last. And one would be concerned, is three months long enough, is six weeks long enough for an OA trial to show adequate efficacy? And should in fact, we have serious -- more serious, long-term studies to clearly assess that.

What is the meaning of an approval of a drug that works for three months? I'm not sure it means a lot in our arthritis population.

CHAIRMAN PETRI: I'm not sure I'm hearing a clear message from the Committee about whether we want to see placebo-controlled trials for these new class of NSAIDs. If I can ask some other people to give their opinion. Dr. Moreland?

DR. MORELAND: I would take a little different view I think, regarding the placebo-controlled trials with these particular, short-term studies.

If they were long-term studies -- six months to a year -- I'd have trouble with that, but with the assumption that none of the non-steroidals actually alter the disease, the patients aren't missing anything except pain relief.

And so if we allowed the rescue medicines

to be taken by the patients and record those -- such as Tylenol™ or other analgesics -- but I think it's important to tease out the anti-inflammatory, adverse events, or physiological events in a trial, and so that we do have a placebo working if it's a short-term trial. That's my bias --

CHAIRMAN PETRI: Your definition of short-term is what?

DR. MORELAND: For OA, six weeks, and RA, three months -- but have a mechanism for rescue analgesics if the patients need them, and record those and record them carefully; but to have that available to the patients.

But I think, we're talking about anti-inflammatory we really need to have a clear control group because we need that for long-term safety.

CHAIRMAN PETRI: Other comments about this placebo issue? Dr. Brandt?

DR. BRANDT: Well, in OA if you --

CHAIRMAN PETRI: Microphone, please.

DR. BRANDT: Looking at OA trials in particular, if you permit rescue analgesia -- which I think pragmatically speaking, we need to do with studies of some duration -- it's no longer a placebo study.

And I think some of that comes through some of the HA studies that produce terrific joint pain relief for months in a saline treatment group. But there was rescue acetaminophen permitted all through the study; makes it harder to evaluate.

CHAIRMAN PETRI: Let me ask Dr. Hyde and Dr. Witter if they could comment on placebo-controlled studies with rescue medication? Pro or con.

DR. WEINTRAUB: Well, you didn't mention my name, but I'll tell you --

CHAIRMAN PETRI: I knew you would jump in.

DR. WEINTRAUB: We're not in the business of making patients suffer, and we do feel as though we're cognizant of, and aware of the need for rescue medication.

Now, the issue of following it and recording it carefully is a very important issue. I mean, it's difficult to record that medication carefully. We all know about pill counts and things like that, which don't tell you very much except perhaps, whether or not the patient dumped the medication in the toilet.

But there are -- so we're perfectly accepting of pill counts. And I know that you can do a study -- in rheumatoid arthritis -- you can do a

study -- or in osteoarthritis, really -- doing nothing but counting the returned acetaminophen tablets. And you know, get perfect results.

Maybe John would like to say something about that.

CHAIRMAN PETRI: Dr. Simon?

DR. SIMON: I would just like to raise an issue that Dr. Moreland raised which relates to actually what these drugs are doing. I am a great believer in where there's smoke there's fire, particularly when we don't know squat about the biologic effects of these drugs, other than some in vitro data.

And I'd like to point out two observations: one by Lipsky, et al, that I know you're quite familiar with -- that's somewhat old by now -- and then a more recent paper that came out in Arthritis and Rheumatism this past January from Australia, that actually raised the issue in very small patient populations that if you look and break the data down into responders versus non-responders in non-steroidal trials, that it seems that responders may actually have biologic effects that we would never have predicted previously.

And we don't yet know whether these

biologic effects are directly predictive of why these patients are responding better than the other patients, because our technology is not that good. In the context --

CHAIRMAN PETRI: Lee -- I'm sorry. Can you -- for those of us who haven't had those articles, explain what the biologic effects were?

DR. SIMON: Not a problem. I actually wrote an editorial on the same evidence. I think that we don't have good markers for activity disease, so with that caveat the biologic markers that were looked at were several cytokines, sed rates to reactive proteins, some effects on white cell functioning, and has been recently identified, there's some evidence that non-steroidals affect leukocyte adhesion so that white cells can't get to the inflammatory site because of inhibition of selecting expression.

So therefore, white cells can't get to the site of inflammation -- theoretically. And in vitro that's probably true in a reproducible basis, both in ex vivo models as well as in vitro models.

Now, I think that, depending what you measure, you get funny responses and there are data that -- there are about ten papers that have looked at these particular issues of cytokine effects of non-

steroidals. A previous non-steroidal in front of this group was tinadat which has had very good evidence that there's some interesting cytokine effects, suggestive of, that may be a mechanism of action of some of these non-steroidals.

Because these drugs perhaps could be used at higher dosages -- perhaps -- because they're not limited in some of their toxic effects, it is possible we may see very different effects of these drugs. I think that Dr. Yocum's observation that we should be clear about seeing two times the dose predicted for utilization, that might be very important from an efficacy point of view.

And I think it would be very lovely if somebody was willing to expend the effort and money to really look at a well-designed -- which has really yet not been done -- a really well-designed, not subset analysis, but a well-designed study to determine whether these drugs will actually affect biologic functions that presently are measurable. And if so, that might be very interesting.

And I also would like to remind everybody that, remember that the ACO responder index was validated against disease modifying drugs, and in fact, we get very substantial responses with non-

steroidal, anti-inflammatory drugs in these measures.

Yes, they are anti-inflammatory; yes, they are analgesic, but perhaps inherent and buried in that observation, is some other effect that may be very important.

CHAIRMAN PETRI: Dr. Abramson?

DR. ABRAMSON: Yes. I think, just to echo these comments, it's always interesting to see what else these drugs do that we don't really talk too much about, that may have profound effects on inflammation.

But I wanted to get back to this discussion of placebo versus comparator, and I'm a little confused and I wanted some help from the FDA, because obviously there's a lot of studies that have been done with the COX-2 inhibitors and thousands of people who have been tested in the trials.

And it seems to me we, as a -- for this discussion, is to sort out what is the purpose of the study that you're talking about. If you just want class labeling as an NSAID-type drug, then there are standard comparators of placebo studies that are currently being done and that will allow approval of these kinds of drugs in the NSAID class.

If you want better GI tolerability it's a different kind of study you have to design, with or

without with placebo. If you want to say you're better than a COX-1 or COX-2 mix, that's another kind of study.

I guess what I'm saying is, I need some clarification as to what the purposes of the different kinds of studies that we're talking about: one for approval, which has a history, and the other for labeling as a COX-2 selective drug, or GI better tolerated drug.

So I think it's the very different discussion as to what kind of placebo controls the programs.

CHAIRMAN PETRI: I think what we're asking is, in terms of efficacy, are we being asked to help design a superiority study, or are we just talking about equivalence to other NSAIDs? Just efficacy; not toxicity.

DR. HYDE: Well, I guess just as far as the basic efficacy goes, the guidelines you've discussed are, you know, we've worked on really still apply to those. So I guess the issues special to the COX-2 -- I guess one question is, if you want to say you're superior to a class, how might you approach that?

Usually we require replication of some

sort. It would be interesting to hear the committee discuss what would be something that would distinguish this from the NSAIDs we know? You know, individual session.

CHAIRMAN PETRI: Well, let's reopen that discussion, because I brought up the possibility of having multiple active comparators -- the mix ratios and the pures. Lee was a little bit down on that idea.

DR. SIMON: No, no, no. I wasn't down on the idea of the active comparators being the traditional COX-1/COX-2 inhibitors that are presently on the market. I think that that raises the issue though, of what you measure.

I mean, for example, if you have a ten percent that may be statistically important improvement of an efficacy of these new drugs compared to the standard drugs, is that clinically important, as opposed to being statistically interesting?

And I'm quite daunted by that. I don't really know what clinically significant means, except for that patients go out and either buy it because it's over-the-counter from a marketing point of view, or doctors use it more frequently because they get less phone calls because patients are comfortable.

How to measure that I don't understand.

And I'm not entirely sure that I understand how you translate that to an experimental study, as to what's clinically important as opposed to statistically important.

Obviously, we all know that 50 percent is better, clinically and statistically, but I'm not entirely sure we'll see that.

CHAIRMAN PETRI: I think one of the points that Dr. Simon made earlier is so important; the game playing with the comparator doses that concern us in clinical rheumatology, and this going to be, I think, a major problem; that the dosing of the active comparators needs to be optimum.

DR. HYDE: Well, I mean, we do have -- you know, there are labeled doses for the NSAIDs that are out there. And you know, a maximum dose would be, what point should we go to, to try to meet the efficacy at the -- at least using the labeled doses?

CHAIRMAN PETRI: I think there are in a way, two separate questions: one is whether a new class of NSAIDs would be superior, and the other question is whether they might be disease-modifying. And I assume that's what you were getting at, Lee --

DR. SIMON: Exactly.

CHAIRMAN PETRI: -- in terms of looking at biologic functions. And I don't think the rest of the committee really had a chance to address that issue. Do we want to mandate or suggest that that be part of the new class of NSAID studies? Dr. Moreland?

DR. MORELAND: I would comment that we don't have the methods to determine biologic effect, whether measuring serum TNF versus some in vitro stimulations of cells to look at TNF as the right biological marker. So I think today, we don't know what biological effect to measure, and I would not put that in as part of the gestalt of this discussion.

CHAIRMAN PETRI: Dr. Harris, do you have any comments?

DR. HARRIS: I would not put in disease-modifying, you know, as a requirement. I'm wondering if one shouldn't say clinically significance, period, rather than disease-modifying, clinically significant in the sense that that is reflected in placebo-controlled trials.

Superior with in fact, you know, comparing -- actually in fact, it's superior to another agent, not a non-steroidal agent. So I'm looking at it from a slightly different perspective, which is you know, effective, and then at superior.

CHAIRMAN PETRI: To get back to what Dr. Simon has suggested -- looking at multiple doses of the new class NSAIDs in trials -- Lee, is that something that you would want to strongly encourage?

DR. SIMON: I think we don't want to raise the bar too high, to be able to make it impossible for future drug development, particularly in this field. However, there are a couple of things that I'm interested in and then the issue is different as it relates to what we would require.

For example, with Larry's comment about the biologic issues, I'm interested in what those would be. I would certainly not require it. I think that structural outcomes in OA need to be defined. Once defined, we need to do those, if we think these drugs may have important biologic effects. And in RA those structural components may also be important.

If we're to truly understand these drugs and their potential from an efficacy point of view, then I do think that we should expect that since there will be tremendous importance in the marketing of these drugs that if they are altering disease, that the companies themselves would be interested in proving that without having to be required for approval.

Unless we decide that superiority -- if that's what we think is important, will then be defined by the fact that it alters structure and function, rather than just function alone. And I'm not entirely sure we can do that because we don't know that.

CHAIRMAN PETRI: Dr. Brandt?

DR. BRANDT: I think we're mixing apples and oranges. There's no assurance that a structure modifying drug is going to be symptomatically effective; certainly for OA. We don't know. But there is an order of magnitude of difference between what it take in terms of resources, to look at structure modification versus symptom modification.

And I would think it enormously problematic to try to define and to shorten the efficacy in terms of structure with the risk of bypassing or overlooking efficacy in a symptomatic sense. Whether these drugs will prove or not to be structure modifying is a terribly interesting question, but it may be for another day rather than at this point.

And I think the first hurdle is to try to focus things -- comparability to what's on the market today, or superiority to what's on the market today --

with respect to symptoms. And the structure issue is around the corner.

CHAIRMAN PETRI: Let me try to summarize where I think the committee is right now. I think there was agreement that these trials should include a placebo group; that we felt comfortable with rescue medication. We all agree there should be -- well, okay. We're going to stop.

All right. We don't feel comfortable with the placebo with rescue medication. Dr. Simon was the first to grimace, so he's the first to comment.

DR. SIMON: I assure you, I wasn't the exact first to grimace, but I'll be happy to be the first to comment.

I think that having worked and looking at Phase II trials as opposed to Phase III trials, I personally am frustrated in the expectation that Phase II trials -- which are typically safety -- have to compare against placebo for reasons that are inherent to the natural history of non-steroidal development; as opposed to really asking questions about efficacy.

Clearly, efficaciously, most non-steroidals are going to be better than placebo. That's really not the question. What we really want to know is whether they're better than what's out

there on the market.

So I think from a safety issue there's some issues about placebo that are important. From an efficacy point of view, once you do one Phase II trial where you've shown some dose effects and whatever, or two, I'm not entirely sure that we should require that in real efficacy trials, because what we really want to know is, they're equally or better than what we presently have.

CHAIRMAN PETRI: Okay, now there were other grimaces, so Dr. Yocum.

DR. YOCUM: I feel again, strongly against the placebo concept. I think that -- I guess if you want a great basketball team you go out and you play the worst team you can find and then say, look how great we are, and you look fantastic. But once you go up against a good drug you've got problems.

And again, I think that in a placebo-controlled trial, having done these over and over and over again, the patients that come to a placebo-controlled trial have less active disease because they're up against that problem.

So that you're now taking a less active patient, you're saying -- and again, the dosage issues played with constantly are at issue. I think we would

be better taking into account Lee's comments about the comparable dosage, to define comparable dosages of the active comparators; i.e., instead of going up against 500 milligrams of Naprosyn, maybe we should define what an anti-inflammatory dose is and what a comparator should be.

But I, again, being more of a patient advocate but also wanting the drug back at the clinic to really work, I'm not sure that better than placebo for three months is all that great. It may be like going up against a bad basketball team.

CHAIRMAN PETRI: You feel the same way about both RA and OA? You don't want placebo for either?

DR. YOCUM: Yes. I feel even more strongly about RA.

CHAIRMAN PETRI: And let me turn to someone who has a slightly opposite point of view. Dr. Moreland, can you summarize how you felt about a placebo?

DR. MORELAND: Well, I disagree with him. I think -- again, I'm coming from the pure standpoint, when we're done with that study I'd like to have as pure data as possible to tease out some of those minor differences that we would like to see.

Again, I share some of the some frustrations that Lee and David expressed by trying to have patients put into clinical trials. So I would favor the placebo arm for the purest standpoint and I think it's doable, and I agree with the constraints that have been listed here.

But to compare this with other trials that have been done, that we do with disease modifying drugs and with biologic agents, Phase II trials typically have a placebo arm. And so we have a 3-month arm there where we have no treatment, basically, no therapy with RA, and we have that hurdle with disease modifying drugs. Do we have that same hurdle for non-steroidals?

CHAIRMAN PETRI: Dr. Liang?

DR. LIANG: I think I see this in a slightly different way. I think the question that's most relevant clinically is really posed in the sense of an equivalence trial. Does this -- these new family of agents work as well as what we have to compare them to by the Helsinki and Nuremberg convention -- the practice in the community.

And I also see this as an effectiveness rather than an efficacy trial in that regard, in that I don't think you should be constraining the control

group with respect to what they get by their current physicians for whatever disease.

And what we're hoping for is that they'll have the same buzz or no worse, and that there will be less GI bleeding and emissions. And then it will be interesting, I think, to do a real efficacy trial at some point, but I think that's another question, another day, another study.

CHAIRMAN PETRI: Okay, let me ask -- before Dr. Harris -- let me ask our FDA representatives how you would feel about not having placebo arms.

DR. WEINTRAUB: Some years ago when I was in academia, I ran a meeting with members who were interested in ethics and biostatistics, and -- people from the FDA. And the people from the FDA were adamant about the weaknesses of active control trials. They said oh, you know, we'll have all kinds of detriments to the data and it will be dirty and we can't figure it out.

Well, to a certain extent they were right -- at least now that I'm sitting on this side of the fence -- I believe. But look, we can have small placebo groups. Now again, that bothers me from a statistical point of view but we can have small

placebo groups.

We can have mini-doses of the -- or, several doses of the test drug. We can do a dose response of the test drug -- and we do that sometimes. And as I say, we have small placebo groups as well. We can do in the same study, arms containing various comparators -- two or, you know, as many as we can convince somebody to do.

We can have different doses of the comparators or just one dose of the comparator -- a standard dose. So all those things can be done, and we are trying to do them right now.

Now, I noticed that Dr. Hoch had something to say about small placebo groups.

CHAIRMAN PETRI: If you could come to the microphone, please?

AUDIENCE PARTICIPANT: I think we ought to look at the RCS Guideline which is E9 document and it explains all the concept when we're doing clinical equivalence trials. There are some issues at the clinical equivalence trials.

The issue is the issue of validity. You know, if you are showing that the test drug is equivalent to a reference drug, is that trial valid? If we have a placebo and if the reference drugs beats

placebo than the trial is valid for establishing clinical equivalence.

So I think, you know, if you don't have a placebo you don't know -- maybe your reference drug is, you know, the patients were not treated right, they did not take the right dose, you know, they're similar to placebo.

So I think that's another part of the coin when we are looking at the clinical equivalence trials. So there is no problem when you want to prove that your test drug is better in superiority trials, so that's okay. But you drop a placebo and design the clinical equivalence trial, we have to be very careful when we get the data how to analyze statistically, the results.

CHAIRMAN PETRI: Let me ask for some comments from the audience. Dr. Geis, Dr. Palmer, do you have opinions about this issue of dropping placebo arms?

AUDIENCE PARTICIPANT: Sure, I have comments. Concerning the ability to do placebo-controlled trials for compounds for treating signs and symptoms, it isn't a problem.

Patients will participate in a trial as long as they understand that if they are on placebo

and they are not getting effective treatment, they can withdraw from the study without prejudice; that they will receive adequate care up to that time.

And one of the measures of efficacy we use is, the incidence of withdrawal due to lack of efficacy. So that seems to work quite well.

In terms of a couple of the comments that maybe you get a different population in patients who would roll into placebo trials, I don't think our data supports that.

When we compare the basic demographics of placebo controls versus studies that are just active control trials, we see basic demographics and we also -- in the studies that we do, we typically flare the patients. The amount of pain or the amount of flare they get isn't any different whether it's a placebo control or not.

So I think you do get representative patient populations or a representative sample whether it's placebo-controlled or not. I always find that in the placebo control it really gives you a clear answer. You can really see whether your compound is working when you have that placebo in there.

When you have an active comparator you're always sort of wondering, well, you know, did the

active comparator really perform the way it should have? Because when you do a lot of these studies over and over, sometimes the active comparator doesn't perform the way everybody thinks it does.

And if you compare yourself to something that doesn't work, well -- or if you look better than something that didn't work too well -- I'm not sure you have an answer.

So I guess in summary, we are able to do these studies. Patients do participate as long as it's understood that they can withdraw if they do not get adequate control. And I think the data does give a very clear answer of what your compound is doing.

But in a placebo-controlled trial I also think you should have an active control as well, so you basically need at least three arms: a standard NSAID in this case, your new compound, and a placebo.

CHAIRMAN PETRI: Let me, while you're at the microphone, ask you a question that obviously the committee is grappling with. Is industry interested in a new class claim of superiority for the COX-selective NSAIDs, or are you looking just for equivalence?

(Laughter.)

DR. WEINTRAUB: He can take the Fifth

Amendment on that if he wants to.

AUDIENCE PARTICIPANT: I think we would be trying to demonstrate the clear medical benefits of any compounds. If it could be superior to NSAID, by all means, we would try to prove that. But our designs are really based on what we've learned from the pre-clinical pharmacology studies.

And if those studies basically have told us, you know, that there is no reason at a certain point in time to expect superiority to NSAIDs, well you'll design your clinical trial to show similarity. But on the other hand, we are not opposed to trying to look for advances beyond the typical NSAIDs.

And I think it was suggested by a couple of folks that maybe you could push the dose of specific COX-2 inhibitors and get disease modification, because you can go behind the side effects of non-selective inhibitors.

CHAIRMAN PETRI: And also, as the dose is pushed -- as Dr. Simon mentioned -- we on the committee are very interested in whether there are biologic effects as well. Other comments from the audience? Always please identify yourself.

DR. NEEDLEMAN: Dr. Needleman from Searle. Your discussion is reasonable as you've isolated

efficacy, but we must go back to the combination of efficacy and safety. And the primary focus is -- and the question I think you should ask is -- can you achieve full efficacy with full safety? And that's a primary focus.

So indeed, even as you talked about correctly, the issues of doses of comparators, you have to achieve -- I think, the responsibility is -- both the prevalence of the comparators for their side effect profile -- such as endoscopies and outcomes -- and their efficacy.

So first and foremost, the first cut at this is, can you fulfill full efficacy, relieve the symptoms, without the burden of side effects? So that's point one.

Point two about comparators. Unfortunately, there is no such thing as a pure COX-1. The comparator pool has to be the existing NSAIDs which are all mixtures of COX-1 and COX-2, and the contemporary belief is that the efficacy in both osteo and rheumatoid arthritis is driven by COX-2, whereas the burden of side effects comes with COX-1.

So your comparator pool -- and I think it's reasonable -- the level of side effects in existing agents that have both are going to be the

adjustment of that ratio.

So I think industry is interested -- full efficacy, safe, and the hope is that these new generations of compounds, you'll even, eventually be able to get to higher efficacy.

CHAIRMAN PETRI: Thank you. Dr. Fernandez-Madrid?

DR. FERNANDEZ-MADRID: I think I would like to go on record that I would favor the introduction of a placebo study. And particularly in the adverse effects evolution of the drug. That is, I would not be satisfied with the conclusion that *X* drug will have a decreased incidence of major events compared with other non-steroidals.

I would like to see how does it compare with placebo? And as it approaches to placebo in terms of adverse effect, I would be much happier.

CHAIRMAN PETRI: Now, I'm not sure we're going to be able to reach a consensus on the issue of the placebo arms. Yes, Dr. Simon?

DR. SIMON: I would like to kind of mirror the two comments that have just been made, specifically as it relates to, I think we're trying to do something that's impossible. Meaning, our charge in this particular discussion was a discussion: is

placebo required for an efficacy trial?

But in fact in reality, these trials are not ever just efficacy and/or just toxicity. And as a result, since the only way we really can understand the toxic effects of these drugs or any drugs, is to be able to initially have some experience with placebo, comparatively.

Therefore, invariably there will be placebo in an arm of some of the studies -- particularly pivotal studies -- to be able to prove safety and efficacy. So --

CHAIRMAN PETRI: You're switching sides.

DR. SIMON: No, no, no I'm not. If I was just to theoretically think about efficacy, which I thought was the question, then I am not sure that I need a placebo arm in this drug class, looking at signs and symptoms.

However, in real world when we're dealing with real studies, I can't see separating safety and efficacy so therefore I would support the use of a placebo arm in those trials.

CHAIRMAN PETRI: This might be a good time just to take a vote on this, and I think the best way is -- oh, one more comment from the audience.

DR. SILVERSTEIN: Yes, Fred Silverstein

from Seattle. Just a comment to amplify what Lee just said. I think -- in fact, in both endoscopic trials and in outcome trials, a real effort is made to look at the population at risk.

So although what Dr. Yocum said, that some of the early trials are done in very healthy people, very quickly the design is going over for any agent to look at old folks who have arthritis, who have co-morbid disease, who may be on anti-coagulants, where a lot of these factors are very important.

And so -- and that's true, both for the endoscopic studies -- because these studies are done in patients with arthritis and therefore I think the conclusions there are appropriate to the target population -- and outcome studies where they're also done in patients who have a lot of co-morbidities.

And then it's especially important to have a placebo because you cannot assume that there isn't some effect -- either an ulceration or ulcer complication. They are not totally healthy patients; they have lots of co-morbid disease.

And so I think in that circumstance, what Lee said was spot on: you've got to have a placebo group so you can compare how your drug is doing -- not only to other compounds but to placebo alone.

Otherwise you could really misinterpret the data.

CHAIRMAN PETRI: Thank you. Now, I'm going to start at the left-hand side and I'm going to ask people, really just to vote yes or no, on whether there should be a placebo arm in efficacy trials.

And I'll start with Dr. Pucino.

DR. PUCINO: I feel there should be.

CHAIRMAN PETRI: Dr. Moreland.

DR. MORELAND: Yes, for both RA and OA.

CHAIRMAN PETRI: Ms. Malone.

MS. MALONE: Yes, for both.

CHAIRMAN PETRI: Dr. Harris.

DR. HARRIS: Yes, for both.

CHAIRMAN PETRI: Dr. Katona.

DR. KATONA: Yes.

CHAIRMAN PETRI: Dr. Yocum.

DR. YOCUM: I'll be the oddball. No.

CHAIRMAN PETRI: Dr. Abramson.

DR. ABRAMSON: Yes.

CHAIRMAN PETRI: I vote yes. Dr. Liang.

DR. LIANG: Yes.

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: Yes.

CHAIRMAN PETRI: Thank you, Dr. Simon. Dr. Brandt.

DR. BRANDT: Yes.

CHAIRMAN PETRI: Dr. Callahan.

DR. CALLAHAN: Yes.

CHAIRMAN PETRI: Dr. Fernandez-Madrid.

DR. FERNANDEZ-MADRID: Yes.

CHAIRMAN PETRI: So we have, I believe, reached a consensus with one dissention.

DR. WEINTRAUB: It depends on the basketball team. We all know what happened to the University of Arizona.

CHAIRMAN PETRI: I have to tell you that there are two more people who do need to vote. So, Dr. McConnell.

DR. McCONNELL: Yes.

DR. LAINE: Yes.

CHAIRMAN PETRI: Okay. So there is still just one dissenting vote.

Now, in terms of the second issue about the active comparators, I think the point that we had reached was that we would be satisfied with one active comparator. But Dr. Simon, I think you suggested in the OA trials there should be both an active comparator NSAID and an acetaminophen comparator?

DR. SIMON: Well, I think that -- I think in OA, since the standard of care today includes both

simple analgesics and non-steroidals at various different dosages, I think that for a superiority claim in the treatment of osteoarthritis, I think it's important to be better than active, non-steroidal comparators.

And to be a better treatment you'd have to prove that you're better than the other treatments that are presently out there for the treatment of osteoarthritis. I do think if we're going to raise the bar to be structure -- which I'm not ready to do -- then that changes the whole ballpark. When we're talking about signs and symptoms I don't think we have any choice but to -- I don't think we have any choice but to do that.

In RA, I would still not like to rely upon just one active non-steroidal. And I think that in RA it would be useful to recognize that there are a group of non-steroidals that are popular and we should look at those that are particularly used from an incidence point of view, and study against those if we're going for superiority.

If we're just going for equal efficacy, then perhaps I could be convinced that one, traditionally used and highly accepted, would be acceptable.

CHAIRMAN PETRI: So the issue on the table right now is whether for a superiority trial we should have two active comparators based on current marketing.

Are there other comments or thoughts about that? Dr. Abramson, first.

DR. ABRAMSON: I apologize because I'm still confused about this issue. If one of these drugs get approved, we're not talking normally about post-marketing labeling in terms of superiority? Is it not up to the corporation to decide whether we need to -- want to show itself better than acetaminophen or street comparator drugs? I need some clarification because that --

CHAIRMAN PETRI: Let me ask Dr. Weintraub and colleagues for a clarification for Dr. Abramson.

DR. HYDE: Yes. For an approval you wouldn't have to prove yourself better than something. That would be an option. But I guess we'd like some guidance on what should be the criterion of this --

DR. ABRAMSON: But if you then choose to want to show yourself better than another drug, then is that the option of the corporation, is that true?

DR. WEINTRAUB: It is true to a large extent; however, there are some conditions where, if

we believe that an active comparator is important, we'll frequently advise the company to include an active comparator in its trial, along with a placebo group and several doses of their drug.

CHAIRMAN PETRI: So what Dr. Simon has suggested is that a superiority claim should be held to a higher standard with two active comparators. And I'm just asking for opinions. If there's strong disagreement, if that's something you would be willing to support. Dr. Moreland?

DR. MORELAND: I guess the question is, why we would use two comparators for a superiority and one for an efficacy. I'm not clear from Lee's standpoint, as to why there would be a difference.

And then if we chose that group of drugs, what are those? Or is that left up to the current standards at the time the trial is designed, and we would say what those are and these are the comparators that you must use -- one of these three or all three of these?

So those are the issues I'm not clear about.

CHAIRMAN PETRI: You know, I brought up whether people wanted to sort of think of the ratio to COX-2/COX-1 in picking those active comparators and,

you know, I think we've been told that that probably isn't going to work. Dr. Pucino?

DR. PUCINO: Yes, my concern with that is that you could take any group of non-steroidals, any chemical class, and they're different -- each one is different based on kinetics and dynamics.

My concern is this new class of agents are going to exhibit the same type of effects.

CHAIRMAN PETRI: Yes, Dr. Brandt?

DR. BRANDT: I think the issue with OA and RA are different in this respect, to whether we're talking -- in RA, clearly the comparators we would chose to use would be in an anti-inflammatory dose. OA is a little bit different and I would vote very strongly for inclusion of an acetaminophen arm.

With regard to the NSAID though, there -- it's less simple than it is in RA because there are data that suggest that number one, clearly, the GI side effects of NSAIDs are dose-dependent, and especially in the elderly; and number two, that the analgesic effect, the symptomatic benefit from treatment with an NSAID in OA in many individuals, is no greater with an anti-inflammatory dose than it is with an analgesic dose.

And because you can anticipate this

difference in side effects, to add an NSAID arm in an OA study, I think it would be important that that NSAID is used in an anti-inflammatory dose and not in a dose that's lower -- where efficacy may be comparable to acetaminophen and side effects would not be terribly different.

CHAIRMAN PETRI: Dr. Laine had a comment.

DR. LAINE: It seems to me inappropriate to ask for one, two or three comparators. It seems to me it's a labeling issue on, whatever the company chooses to compare to that's what they're going to get a label for, it would seem to me.

So if they're going to compare it to one, get a label for one or for two, I mean, I would ask the FDA people that, but it seems to me that's the issue. So to require them to have to do two, if they show it's better than one drug in two good studies they get a label that says it's better than that drug.

Is that not correct?

DR. HYDE: I guess the simple, comparative claim would be a replicate of, you know, superiority to a specific product. If you do two studies compared to drug *X* and you're better then that would get you that claim.

And you know, that's something that could

be entertained here. I guess we were sort of hoping you know, to discuss the broader issue. Could you get superiority -- and this can apply equally well to the safety issue when you come to a class -- and how it should do that without studying every single thing in the class.

The best marketed, the recognized superior one by some criteria, or some representative sample, or, you know, we'd just like you to discuss those issues if you think that's even a feasible objective.

CHAIRMAN PETRI: Well, we've been trying. I think the issue is whether if there's a new class of NSAIDs, is it possible to design a superiority study without multiple comparators? And we've had Dr. Simon's suggestion that the comparators be based on marketing; we've had a similar suggestion from me that it perhaps could be based on ratio of COX-1 to COX-2.

Are there other thoughts about comparators? Dr. Abramson.

DR. ABRAMSON: I think that the fundamental problem is that you have so many non-steroidal drugs on the market available at different doses, that there really -- I don't think you can a priori design a -- a group of people like ourselves mind you, could not design a group of representative

comparators that then a new drug could be pitted against, against a class.

I mean, I think there are some standard, historical reasons that a group presented some drugs that they used to get approval. And then I think it really depends in a post-marketing sense, how these drugs could come -- go head-to-head. But I think that becomes a corporate decision, in my view, because I don't think any of us would agree on what the three representative NSAIDs could be.

CHAIRMAN PETRI: Or even whether it's two, three or four. Dr. Liang.

DR. LIANG: I think the more prescriptive we get in terms of specifying the comparator, the less useful it will be in real life, and that I really think that this is maybe an opportunity to do with this continuation trial.

OA patients were happy with whatever they're getting and then they stop it, because we know that from other studies, that some of those patients are still pretty happy, even after they discontinue an allegedly, effective agent. And then randomize them to anything basically, and the COX-2.

Because I think that it would be -- I don't think there's any rhyme or reason for the NSAID

du jour, and over the life of an OA patient they inevitably tried them all. So I think it would be more useful to me as a reader to have known that a trial, you know, sort of pitted themselves against real life and came out the same with less problems.

CHAIRMAN PETRI: Okay. Well then to summarize -- I'm sorry. Dr. Katona.

DR. KATONA: Just one more issue is the dosing. Coming from Pediatrics it makes a big difference what dosage I'll be using for the children, and just would like to bring up a clinical example.

We usually use Naprosyn between 10 to 20 milligrams per kilo for children. And I could tell you that tremendous differences as far as control of the inflammation in JRA between 10 and 15, and 15 and 20. It you would take someone and compare an optimal dosage of the new drug to a 15 of Naprosyn, that would not satisfy me.

So it almost looks like you would have to use like more than one concentration of the comparison drug as well as the new class of drugs for me to really buy that it's superior.

CHAIRMAN PETRI: Okay. Now, to summarize where I think we arrived, we all want at least one active comparator in an RA trial. In an OA trial we

want an active NSAID comparator at anti-inflammatory doses and acetaminophen.

Were there any comments about that summary? Any disagreement? Let me ask Dr. Weintraub if there are any other important issues that the agency wanted us to discuss in terms of efficacy, question one?

DR. WEINTRAUB: Well, I don't really think so, except that question one can also be applied to the toxicity questions -- both to the efficacy and the toxicity questions. I think we've been around it pretty well.

Don't forget that we put in your book of reading materials the letter from Lucy Rose and Linda Katz about the issue of comparator studies. I mean, it's not as if we haven't thought about that a fair amount of time and -- spent a fair amount of time studying it. It's from 1994 but it's still valid.

And I'd like to say to Dr. Liang that some companies do do studies with all comers -- with whatever non-steroidal their doctor and they decide to put on. Not necessarily in this field but in any field, or in many fields.

But I think we've gotten what we want out of the committee for this question.

CHAIRMAN PETRI: I think that's a good point to adjourn for lunch, and we'll reconvene at 1:30.

(Whereupon, a brief luncheon recess was taken at 12:30 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:36 p.m.

CHAIRMAN PETRI: We have a major charge for this afternoon. We're going to be talking about the toxicity issues. And they're divided in our list of questions between GI and then what I'll call other: renal, bone, reproductive toxicity.

I want to read the first GI question because I think it's one of the most essential. "What constitutes the type of adequate and well-controlled study or studies which will support changes to the NSAID GI Warning?"

And we're given two sample discussion points: large and simple, and endoscopy. And I think really what we're going to be talking about is endoscopy versus clinical studies.

Now, I know many people had strong opinions this morning, and perhaps I could start with Dr. Laine, and if he could summarize where he stands on this issue?

DR. LAINE: You mean the warning about the two to four percent PUB kind of warning?

CHAIRMAN PETRI: Well this is really right now, just talking about the type of studies we as a committee believe are important.

DR. LAINE: Well, I guess I would view it as three different types of -- I mean, there's three potential type of studies I think we could do. One could suggest I guess -- you can never mandate in the FDA -- but I think one, dyspepsia studies would be interesting and potentially important to me.

And they could be kind of outcome studies that are not -- do not have to be endoscopically-based. I think endoscopic-based is interesting but I think in order to get -- I don't think it's mandatory, in my view. So I think dyspepsia is a very interesting and important issue to the patients, not related to the complication issue.

The second are obviously the endoscopic studies, which I think still have some importance as we've heard from a lot of people in terms of, I think they are at least somewhat predictive, albeit it very poorly predictive of the clinically important outcomes.

But I think that part of the problem is all -- in the past all of the indications that have been given have been given on endoscopic studies. So I'd be interested in what one would do if you didn't have endoscopic -- if you wouldn't allow somebody I guess, to do endoscopic studies to get the same

indications that people previously have gotten indications for with endoscopic studies. So I think that would be a potential concern.

And I think the final type of study clearly, are just the outcome studies, and again I don't -- although it's very interesting to have endoscopy in those studies, I don't think it's important because what you really care about are the clinically important endpoints.

And in those you could just mandate endoscopy at a minimum when the patients developed these kind of symptoms or signs that were written in the protocol already requiring endoscopy. You know, if they have a certain degree of bleeding, if they have symptoms of perforation, severe pain, those kind of things; you would mandate endoscopy on those.

So I mean, in my view there's three, different potential types of studies, and I guess you need to decide what exactly the claim and the endpoints you're looking for.

CHAIRMAN PETRI: Can we explore the first one, dyspepsia? You separated that from the clinical outcome study, I assume because it would be a very short-term study. How long should it be?

DR. LAINE: Well, it could be shorter

term, but more importantly it also might -- well, it's a harder study to do because -- I mean, it's a very subjective endpoint, and dyspepsia studies can be very difficult to do, if anybody's done those studies.

But there are now -- well, there are instruments for dyspepsia; there aren't any instruments to my knowledge necessarily, for NSAID dyspepsia, but there are instruments for dyspepsia. I mean, the question would really be, I think that you would have to do it for some period of time. I mean, I don't know whether three months or one month; I'm totally making that up.

CHAIRMAN PETRI: Are there any clinical studies of dyspepsia and NSAIDs? How long were they?

DR. LAINE: There are studies but there are just a number of them and a lot of them aren't very good. The ones that were just in The New England Journal, they actually had some -- they had a number of different things. They said, just have mild -- they broke it into mild, moderate, severe -- and just said, success was mild or none.

Most people I think who do dyspepsia trials wouldn't really think that that's a very reasonable -- a 3- or 4-point scale is probably not a very reasonable way to go for dyspepsia. And those

were rather long-term studies.

It would depend also, whether you're talking about which group of patients you're talking about. If you're talking about people who don't have ulcers or people who have NSAID ulcers and you're following them.

CHAIRMAN PETRI: I would say in rheumatology we'd want to put all the co-morbidity in there such as whether the person's on prednisone or methotrexate as well.

Let me ask, just thinking about this idea about dyspepsia studies, other comments from the committee? Ms. Malone, can you comment from a consumer's point of view about a dyspepsia study?

MS. MALONE: Well, obviously you'd like as much control and thoroughness, but it's a subjective thing too. You know, you have to have some definition somewhere. I don't --

CHAIRMAN PETRI: Well, would that be important to the consumer? The claim that, oh, new NSAID --

MS. MALONE: Yes.

CHAIRMAN PETRI: -- is causing less dyspepsia than old NSAID?

MS. MALONE: Yes, but what do you mean by

"less"? How do you define "less"?

CHAIRMAN PETRI: Well, that has not been defined as far as I know. Dr. Laine?

DR. LAINE: I'm not saying it's necessarily easy to do, but if one develops and "validates" an instrument to measure just on the surface, it seems to me that it's a very important thing to our patients because what do they complain of most? The pain with NSAIDs I would think.

And if you had a product that you could legitimately show caused less pain or no more pain than placebo even, that to me would be, I would think, a very meaningful finding and a very meaningful indication.

CHAIRMAN PETRI: Dr. Fernandez-Madrid?

DR. FERNANDEZ-MADRID: I'm not opposed to a dyspepsia study. I think it would be very important for the drug company and for the patients. I think dyspepsia is one of the main reasons why patients switch from one drug to another.

But we are talking about changes in the non-steroidal GI warning, and I don't think that we would change the GI warning by the data on dyspepsia. I think we need to look at the major events -- massive GI bleeding, ulcers, perforation -- to change this

labeling.

CHAIRMAN PETRI: Well, I assumed we were asked the question because it might lead to a change in labelings. Let me ask Dr. Weintraub what the possibilities are.

DR. WEINTRAUB: Sure. There are two main possibilities. One is that we can change the clinical trials section of the label; that is, the place in which we describe the studies that went into providing the data that we are putting in the label.

Or the much harder, more difficult, higher barrier -- whatever you want to say -- would be to change that GI warning from the template that we have. That is, right now it is the class labeling for these compounds.

CHAIRMAN PETRI: Dr. Simon, comments on dyspepsia studies?

DR. SIMON: Well, what I'm interested in knowing in this discussion is, Loren, would you have actually any idea to require a dyspepsia study for approval?

DR. LAINE: No, and by the way, I was not suggesting that it's more important than the clinical outcomes. I was just saying in my mind there are three different types of -- separate types of studies.

I would agree with Dr. Fernandez-Madrid that obviously, if you want to take away the important complication GI warning it's not related to dyspepsia; it's related to the outcomes such as bleeding and perforation, hospitalization.

I was really just raising the issue of three different types of studies in my mind.

DR. SIMON: But how about let's push the envelope a little bit more? We've already had the discussion that this is perhaps a different class. Why are we entertaining a discussion of even discussing the use of non-steroidal class labeling with drugs that might be very different?

What in fact, makes us think these are the same? I mean, we've entered into a discussion here with a burden that I'm not entirely sure I understand, and I'd like to know the evidence that anybody can present to me here, that tells me we should be discussing it in this manner.

Perhaps we should be asking the question -- again maybe -- what are these drugs doing, what are our expectations based on pre-clinical data as to what they might do to patients, and to design those trials that will be best able to demonstrate the safety of these agents in their use in the treatment of patients

with pain and inflammation?

I'm just not entirely sure I understand why we're even discussing the issue of class labeling of non-steroidals. There is evidence that these aren't the same. Maybe we should discuss that first -- maybe, maybe not -- and if we're not going to discuss it first then I think we have to ask a different question.

And the different question has to be, we can't create a new bar. If these are going to be considered exactly the same as non-steroidals then what they have to do is prove that they are another non-steroidal, and maybe it perhaps should be a marketing issue and post-Phase III to prove that they're something else. And then that relates back to the dyspepsia.

It certainly it would benefit the company to have a drug that causes less dyspepsia, and that could be done later. I think that we still need to grapple with the other issues which I think are really critical.

DR. WEINTRAUB: The reason why we consider -- why we're talking about the template, the GI warnings -- is because we have to start somewhere, and we start with those.

And if it really does -- if it is a real -- if they are a real separate class, something different, something else, something that's so totally different that it deserves a different template, a different warning, a different precaution, etc. -- we're willing to accept that. We're starting with the fact that these are, until they're proven otherwise.

DR. SIMON: What would be required to prove them otherwise?

DR. WEINTRAUB: Well, to a certain extent, that's what we're asking you.

DR. SIMON: Well, the reason I bring that up is that the pre-clinical data would suggest that they are otherwise. So if we didn't have all the baggage related to non-steroidals and 15 me-too drugs that the FDA's had to contend with for God knows how long -- each one coming in and claiming something -- if we didn't have all of that and we suddenly had a drug that biochemically and biologically behaved this way, I'm not entirely sure we'd be discussing it like this.

DR. WEINTRAUB: Well, we might not. If we didn't have all those other compounds -- I think there are 19 -- we would be discussing this as a de novo type of drug. But unfortunately, we have the baggage.

So we've got to get rid of the baggage if we can.

CHAIRMAN PETRI: Let me ask Dr. Simon, you do not object to dyspepsia studies?

DR. SIMON: Oh, no. I think that without making the bar higher and without the issue of the regulatory function of approval, I think a dyspepsia study would benefit my patients dramatically. The idea of knowing that something doesn't cause dyspepsia would be great, and gives anti-inflammatory and analgesic activity. I think that would be great.

CHAIRMAN PETRI: Let me also ask the committee for other feedback on a 3-month trial for dyspepsia. Does that seem reasonable? Any comments?

Okay, let's move on to the second proposed study which is the endoscopic studies. We have multiple issues to discuss here such as whether an endoscopic study could stand alone; whether it always has to be tied to a clinical outcome study; how long it should be; how often; endoscopy by a certain time period, on the basis of symptoms and signs.

Dr. Laine, do you want to elaborate?

DR. LAINE: Well, I mean, I think you can't really tie it to clinical outcomes because it's a different study. I mean, I would either have a --

CHAIRMAN PETRI: I mean, I'm asking

specifically, can an endoscopic study stand alone as a claim of less toxicity?

DR. LAINE: Well, I mean, it probably depends on the wording. I mean, in the past I think, some parts of the agency have actually given a claim for less complications on the basis of less endoscopic ulcers. So I think, you know, I'd have to look at what's happened --

CHAIRMAN PETRI: That very important subordinate clause there.

DR. LAINE: No, I know there is, and that's why I'm saying that. But that is actually the case. So it becomes a problem about new versus old labeling. I would think it makes sense to just, if you have an endoscopic study to certainly say that it decreases non-steroidal associate ulcers.

The question is, are you willing to take the one mucosa trial as enough to say that it also decreases ulcer complications? And I think that may be a big leap.

CHAIRMAN PETRI: Let me ask Dr. Moreland for his opinion about endoscopic trials.

DR. MORELAND: Well, I think we're going to have to accept that the endoscopic findings are the surrogate we have. And having the hurdles of

Misoprostol and other drugs, have certain hurdles of using that as their provability, that we should consider the same type of trials for the provability of a COX-2, less GI toxicity than others.

So I would be in favor of the endoscopy studies that were similar to those that we used in the Misoprostol studies, and that's the best surrogate we have for long-term outcome. And use that as a sole indication as to whether the drug gets improved -- gets that safety profile.

CHAIRMAN PETRI: Specifically, it would not then require a clinical outcome study? That's when I mean by an endoscopy study standing alone.

DR. MORELAND: My initial thoughts -- which may change after other user presented, but it would stay alone, because I think we have to -- if we're going to take the leap of faith that that is our best surrogate marker, let's do that.

If a company would like to go ahead and pursue that 10,000 patient study to substantiate that claim, then that would help us a clinicians to decide whether we felt that that other study was final.

I would perhaps ask two studies -- two clinical studies then, with the endoscopy studies as the studies.

CHAIRMAN PETRI: And before I go to the audience, if I could ask Dr. Laine to comment about the study design of an endoscopic study. Should it be monthly endoscopy, should it be endoscopy based on symptoms and signs?

DR. LAINE: I mean, I think doing the straight endoscopy study it wouldn't be based on clinical science. It's going to be when somebody has certain clinical signs like bleeding or severe pain causing them to be unable to do anything, then they wouldn't get endoscoped. But in general I think you would have regular endoscopies.

One can argue -- I don't think I would do it every month, personally. The questions is whether you do three months, which is what people have done; whether you do six months. We know that -- it seems that somewhere at three to six months it starts, by the information we have, the number, the incidence of ulcers starts leveling off.

If you do a 3-month study I think every month is reasonable. If you do a 6-month study I don't think every month is reasonable.

CHAIRMAN PETRI: So you just zero, three, and six?

DR. LAINE: Or maybe, you know, one-and-a-

half, three and six; something like that.

CHAIRMAN PETRI: Let me ask other opinions. Dr. Simon?

DR. SIMON: I have a question to ask for further clarification, for both Loren and Dr. Moreland. In your construct of these studies, a) there would be an active comparator arm, right, where there would be a placebo arm? And in addition, would you select out your patients?

Would you go for the high risk patient or not, and if you chose to not go for the high risk -- if you chose to go for the high risk patient, in the active comparator arm would you feel compelled to use a prophylactic agent in the high risk patient? And then how in the world are you going to power the study to ensure you actually get some useful data out of it? And particularly if it's going to translate into an outcomes component in the long term.

CHAIRMAN PETRI: We'll ask Dr. Laine to respond first.

DR. LAINE: Endoscopy is actually -- an endoscopic would not be that hard because first of all in terms -- starting backwards -- powering wouldn't be that difficult. If you really have an agent that causes very few ulcers and we know what the standard,

active comparator causes, you know, it's not going to require a massive endoscopic study to document that difference. So I don't think that part's that hard.

My view in general is, you want to try to -- you know, as you said, you want to try to be as inclusive as possible and you want to try to include as many high risks as you can. Now, there are certain ethical and IRB considerations that cause you not to be.

You know, what do you do with the bleeding ulcer patient in the past? I mean, that's difficult. What about the non-bleeding ulcer? Maybe you can include the non-bleeding ulcer but not the bleeding ulcer.

I think those are all the big questions that I think -- or fine tuning -- I'm not sure it's worth getting into here, but I mean, you can sit around for hours and days discussing those issues. But I would try to be as inclusive as possible.

And I don't think it's that hard a study, I mean, in terms of the sample size. Just because, if you really have a drug that doesn't cause ulcers then you're going to find that difference.

CHAIRMAN PETRI: Two arms or three? Placebo group?

DR. LAINE: I think it would depend on the claim. The other thing we haven't talked about is, do these drugs want to have a claim of just better than an NSAID or do these drugs want to have a claim of, we don't cause any damage at all?

And I think which claim they want to pursue would lead to whether you have a placebo group or not. I don't think if they just want a, I'm better than another NSAID or other NSAIDs, I don't think you need a placebo group. But if they want to say we don't cause damage, you do.

CHAIRMAN PETRI: Dr. Moreland, do you want to comment?

DR. MORELAND: I'll just add a comment about the high risk. I think there's more than one group of high risk patients. I wouldn't want to put the group of patients that are on Coumadin into this type of a protocol. I'd do a separate, smaller study. But perhaps the high risk being those who've had previous GI disease, peptic ulcer disease; put them in. Again, we can define that.

DR. SIMON: An you wouldn't prophylax them, or you would?

DR. MORELAND: With?

DR. SIMON: Whatever you decide would

work, prophylactically. That's not part of the discussion today; I didn't want to get into that. But if you decided that they were high risk, the standard of care today is, in the high risk patient given a presently available non-steroidal, is to prophylax them. And would we not fulfill that part within that protocol?

DR. MORELAND: I mean, I wouldn't think you'd want an -- I mean, you would have a separate arm, or just you'd have a separate arm of high risk patients who all got prophylaxis? I'm not sure that would make a lot of sense for the study.

DR. SIMON: Well, that's my problem in designing this trial. That's why I'm bringing it up. I don't --

DR. MORELAND: I would just think you'd take as high risk as you can without feeling that you're crossing the line and not prophylax them, and just keep them under very careful observation. I mean, if you think they're too high risk you just don't enter them.

But I think the point of giving them the NSAID and giving them Misoprostol defeats the purpose of the study unless you're trying to show that a standard NSAId plus Misoprostol is the same as or

comparable to these new agents.

DR. SIMON: I just feel -- and not to have the last word here, I really don't -- I would feel incredibly uncomfortable in that circumstance. I would have a very difficult time recruiting patients into a study that I knew would put that patient at an increased risk of having a bad outcome -- even in a controlled circumstance -- when I knew I had a drug that will decrease that risk by over 50 percent in that high risk patient.

DR. MORELAND: Well then you just want to include the patients who are at -- patients who are at that high risk that you feel uncomfortable with and others feel uncomfortable, you just probably can't include in this study, then. I mean, you have to be one way or the other, but I just wouldn't include them then, if you feel too uncomfortable.

CHAIRMAN PETRI: Dr. Brandt.

DR. BRANDT: Michelle, back to your question of a moment ago about placebo group, I think that's tough because if you're talking about a 6-month endoscopy study then you've got the efficacy issue with regard to symptoms. They're inseparable.

CHAIRMAN PETRI: Dr. Abramson.

DR. ABRAMSON: I've got a question about

study design. If you were going to use this kind of protocol to get at the predictive value of endoscopy, with the notion that if they've been under power in insufficient numbers and you're going -- what would you do if you found an ulcer at one month or three months? Would that be an indication to drop the patient out of the study based on the month's old data, or putting them on that?

DR. LAINE: I would --

DR. ABRAMSON: With the understanding -- I'm sorry -- with the understanding that you know that 95 percent of those people who have ulcers by endoscopy in three months will not go into a clinically significant event. So as you endoscope them are you dropping them out or are you introducing some --

DR. LAINE: I guess I'd say two things. One, I presume the endoscopic trials -- the endpoint isn't ulcers. They've reached the endpoint when you find an ulcer.

Two, it just seems to me if Lee feels uncomfortable with including somebody with a history of ulcers, I think as I said before, I really just do not believe that any IRB is going to allow you to take a patient who has an NSAID associated ulcer -- that

you see an ulcer there and you say, stay on this NSAID and we're going to watch you with the ulcer. I just don't think that would ever happen.

And I think if you started adding prophylactic there with Misoprostol or proton pump inhibitor or something, it compounds the study, so I'm not sure what you're really getting. So it would be interesting to take those people and put them on a COX-2 agent and see if it had anything to do with ulcer, if it affected ulcer healing. That would be an interesting study. But that's another issue.

CHAIRMAN PETRI: First question from the audience.

DR. T. SIMON: Tom Simon, Merck Research Laboratories. No relation.

DR. SIMON: Is that defensive?

DR. T. SIMON: We've obviously grappled with many of the same questions as the folks across the aisle, and endoscopy clearly -- in our view -- clearly is a reasonable surrogate for an outcomes trial. Endoscopy studies can be properly constructed to reflect the population that's really the one you're going to treat.

They aren't done in medical students. You can study people who have had a history of perforation

ulcer or bleed -- albeit one has to be careful to enroll people carefully, that you --

CHAIRMAN PETRI: Specifically you're going to study those people without a prophylactic therapy?

DR. T. SIMON: Correct, correct. And then follow them closely, and then obviously let them drop if you see an -- let anybody who develops an ulcer drop out of the study at that point and take care of any lesions that happen, of course.

And these trials can clearly last six months, which is a relevant time period, and you can clearly do the endoscopy that's needed, and we wouldn't study medical students in order to try to get such a claim.

The other thing is that, you know, endoscopies don't have to come in a vacuum. There are other ways to look at the rest of the GI tract. I mean, there are surrogate markers that look at the small intestine and look at blood loss along the length of the intestine, and those trials can be done.

And additionally, there are these other short-term studies one can do in normal volunteers. And finally, you can take a look across an entire development program as was mentioned earlier.

You can have an outside board of folks who

evaluate each and every potential perforation ulcer bleed to determine whether or not it's a real event, and you can look at the incidence of those events across the program.

And so when you look at the whole cloth of the endoscopy studies, markers of intestinal damage plus the additional incidence, or the measure of incidence of perforations, ulcers, and bleeds, if that whole body of data is going in the same direction there's enough there to say that this is something different and something that requires the NSAID GI work, and you don't need to have it.

CHAIRMAN PETRI: Before you leave the microphone, can you redefine for us these other outcomes that you think could be associated with clinically important GI problems?

DR. T. SIMON: Yes. I mean, these end up being studies you have to do in normal volunteers sometimes, because of just constraints. For example, you can look at loss of chromium labeled red blood cells. You have to treat for long if you're going to do that and there's some special controls you have to do. And one can also --

CHAIRMAN PETRI: Do you know what the correlation coefficient is with endoscopy findings?

DR. T. SIMON: I can't give you a tight correlation coefficient but I can tell you that it does at least tell you what's happening beyond the level you can reach with the endoscope. It looks mouth to anus and that's an advantage of it, so if there's damage beyond where you can reach you'll see something.

You can also -- going back to the intestinal issue -- you saw that picture earlier of diaphragm lesions. Some people think that that lesion begins with the breakdown of intestinal permeability; such things that ought to stay inside the lumen stop doing so.

And you can measure breakdowns in intestinal permeability by looking at absorption of marker substances such as chromium EDTA.

CHAIRMAN PETRI: Thank you. Next question from the audience?

DR. SILVERSTEIN: Silverstein from Seattle. I actually wanted to address some of the same points but from a different standpoint. The question about whether endoscopic studies are important I think, is an essential question to this kind of consideration.

And in fact, going back 15 or 20 years, we

did a whole variety of studies to look at gastric injury: potential difference, gastric washout, chromium 51 tagged red cells.

And I think it became pretty clear -- and this is a slightly different issue than whether you're looking for damage beyond the ligament of trice so that you're looking at small bowel or colonic damage -- that endoscopy really was the best way to measure damage to the esophagus, stomach, and duodenum.

Now, occasionally the endoscopist may miss a lesion, especially in the case of bleeding where it may be more difficult. But clearly endoscopy I think, has a pivotal role here in defining injury. And if you were to take that away from the development I think you'd really be handicapping the ability to look at these new drugs.

The other comment I wanted to make is that there is a continuum -- although we don't completely understand it -- a continuum from an erosion to an ulcer to a complicated ulcer.

And so what we're saying is, the two places to look for significant data are ulcers -- because that's a doable study -- and I think what we often do, by the way is, we'll be sure the patient doesn't have an ulcer before they come into the trial.

So that's one of the ways you're protecting the patient, even if the patient does have a past history of risk factors.

And you can study what happens endoscopically. I think the data is good that by three months you pretty much know what's happening. I think all the studies I've ever seen suggest that you can tell by three months what's happening. And in four, five, six and beyond it's sort of a relatively flat line.

And the second thing is to do, is to look at the pertinent clinical outcome, and I think that should be done in the population at risk. So you're stuck with the problem of, you know, Lee's question about whether you can do these people, but these are the people who are at risk.

So with all the precautions you can use I think you have to examine what the risk to those patients is. And then finally, when you do a clinical outcome trial, those of you who think that GI bleeding is easy to define haven't ever tried to define it.

It's a very difficult trial to do and that's why we have three gastroenterologists look at every case in an iterative way, get back to the investigator -- it's very difficult.

And we've tried to set out definitions that are really clear but three people -- sort of on a little group -- in addition to people from the company look at these of these cases. Because it's a clinical decision.

But definitely it has to be done in the group of people who are at risk. So I see that the two really most important measurement points are carefully designed endoscopic studies and clinical outcome studies.

CHAIRMAN PETRI: I think before you leave the microphone, can you address the earlier point, which is that the endoscopy trials have more validity if we included a chromium labeled red cell blood loss, intestinal permeability?

DR. SILVERSTEIN: Yes, I actually don;t think so. It's answering a different question. It's answering the question of whether there is damage beyond the ligament of trices -- so further down the gut.

I think if you're asking the question how often does an ulcer occur, that's what you do with an endoscopic study. I don't think you'll get more information about what's happening in the stomach or the duodenum from a chromium 51 tag study --

CHAIRMAN PETRI: No, it was specifically what we get at some of the NSAID toxicity in the small and large bowel that way.

DR. SILVERSTEIN: Well, it's possible but I can tell you that as difficult as it is to determine esophageal -- excuse me, gastric and duodenal bleeding -- it's at least ten times more difficult to deal with the small bowels. It's extremely complicated.

And I think once you add those parameters you're making the studies more difficult to do. So I personally, would favor looking at the endoscopic study for the stomach and duodenum, and looking for clinical outcomes.

Now clearly, the points that Dr. Laine and Dr. Kemmy made this morning, there is damage to the small bowel and colon and you must keep track of that. And perhaps that's where there would be some relevance to looking at chromium 51 tagging.

But I think mainly for the stomach and duodenum it's going to be an endoscopic evaluation. In my opinion.

CHAIRMAN PETRI: Dr. Laine, can I bring that right back to you? how do you feel on this issue?

DR. LAINE: Well, my concern I guess, with

chromium labeled RBCs, with all due respect to Tom, the question is how it would be helpful additively when you're doing the endoscopy. If it's up and you have endoscopic damage, is it from the upper GI track or is it indeed from the small intestine or beyond?

And what its clinical significance is in terms of predicting important clinical outcomes I think, is probably even much less certain than the endoscopic which has obviously, as we know, not complete certainty.

So I'm not sure. I would probably argue more with Fred's point then Tom's point in terms of, I think it's interesting and it's certainly helpful and it's interesting information. Whether it would help me -- and as Tom said, it's one more bit of information about the compound and the class, but I'm not sure it would actually help me in terms of labeling issues, probably.

One other comment. The other issue about these COX-2 inhibitors and the combined inhibitors is platelet function. And clearly, when platelets malfunction they're going to make bleeding tendencies worse. And whether it's from an ulcer or whether it's from an angiodysplastic lesion in the small bowel or colon.

So it's just something to bear in mind. We haven't talked about that today, but I think it's an important part of understanding the clinical outcome to these patients is, are you -- you know, for example, a person who's on Coumadin, you really would be reluctant to put them on an agent which interferes with platelet function. If a drug is free of that it might be okay. So that's an important part of GI bleeding as well.

CHAIRMAN PETRI: Next question?

DR. T. SIMON: Tom Simon again. I just wanted to clarify a technical point. I wanted to make clear that the chromium red blood cell loss and EDTA are separate trials from the endoscopy study. You wouldn't do them in the same trial or the endoscopes would get messed up.

The other thing is that, I do think that the red blood cell does help you if what you're showing is lack of effect rather than some level of effect. And again, it is one more piece of information to help put the whole thing together.

CHAIRMAN PETRI: Any other comments about endoscopy trial design? Then why don't we discuss a clinical outcome trial? I would say the clinical outcome trial is going to be expensive, require a lot

of patience, a long period of time.

Dr. Laine, do you want to comment on whether you think it's important, necessary, should be mandated, should be optional?

DR. LAINE: Well, I would think you would do it as simply as you possibly can to enroll as many patients as you can. And this would really be a more true outcome study where you really try to be fairly inclusive and not too invasive.

So I mean, I would actually just try to enroll patients and randomly assign them to whatever the arms one would decide would be, and just follow those patients for certain pre-defined clinical criteria.

Leading criteria, as Fred mentioned, can you very specifically go through what constitutes a GI bleed, what constitutes severe pain, what constitutes other thing -- obstruction -- and you mandate or suggest endoscopy only in those people who reach the certain clinical criteria, or have these clinical criteria. And you follow them.

And it's really an outcome study looking just at these specific, important, clinical outcomes.

CHAIRMAN PETRI: Is this going to be mandated; is it going to be post-marketing?

DR. LAINE: You mean, is the study going to be mandated in order to get approval for the compound?

CHAIRMAN PETRI: Yes.

DR. LAINE: Well, I think probably not given the fact that it's never been mandated before for approval of a compound. The question would be what the labeling would say. But it would seem to require that; I mean --

CHAIRMAN PETRI: Specifically for a label of better GI safety, is this going to mandated or required; is it going to be post-marketing?

DR. LAINE: I'll take comments from around, because I mean -- I'm not sure that it will be required. I think safety depends in certainly ulcers, and it would depend on how the agency is doing. Like again, they've done ulcers and ulcer complications together in the past, and I've always had a problem with that.

If they're going to continue doing that then perhaps that endoscopic trial would be enough. If they're going to start changing to have clinically important outcomes and ulcers separately, then perhaps yes.

I think practically though, the answer

would probably be no. It wouldn't be required for --

CHAIRMAN PETRI: For a GI safety label?

DR. LAINE: Yes.

CHAIRMAN PETRI: Let me ask other people for opinions. Dr. Brandt, how do you feel about a clinical outcome trial?

DR. BRANDT: I think that's important data to have and I'm not personally comfortable sufficiently using endoscopy as an endpoint. So I'd like to see that.

CHAIRMAN PETRI: You want to see it before that GI safety label goes on board? Let me ask Dr. Simon.

DR. SIMON: Can I ask a question first? Would you screen for H. Pylori infection?

DR. LAINE: What I would do is, I would gather the information but I would try to do a real world study and I wouldn't actually treat those patients because I would not be even evaluating those patients.

I would be just taking patients like you would in an office and just giving them an NSAID and I would gather the information by a serological blood test, but I wouldn't actually treat them or act upon that information.

DR. SIMON: And would the concomitant endoscopy trial beforehand or running similarly at the same time, would you have screened them for H. Pylori?

DR. LAINE: Again, I would gather the information but I wouldn't actually tell the investigators the answer -- unless they had an ulcer at that time.

If they had an ulcer at that time then I think it's important to know, but that would be standard of practice. If they don't have an ulcer I would gather the information but not act upon it, personally.

DR. SIMON: Then under those circumstances I would favor an outcomes trial for registration. The problem is that I -- that's raising the bar I think, than what's happened before. So I think that's entirely unfair and inappropriate.

But on the other hand, my gut feeling is what we really, really want to know is, is this going to be a different drug as far as outcomes go? But on the other hand I recognize in the real world, this is a really big deal, a really big effort, and I've complained about the mucosa trial.

I was unhappy about some of the ways that was designed, and that was incredibly expensive. I

can't even imagine what would go into a really well designed protocol, to answer that particular question.

So that from perspective, I think it's unfair to require it, but I would certainly like to have it.

CHAIRMAN PETRI: Well, if you don't -- you're sort of schizophrenic here.

DR. SIMON: Not only here. I'm saying I'd like to have it as a trial. I don't think it should be required for registration. I think that could be done as -- but I think it would be very useful information for my patients. It's not schizophrenic.

CHAIRMAN PETRI: Dr. Liang, do you want to come down one side or the other on this issue?

DR. LIANG: I vote the same side. I'd like to find out about the dyspepsia. The endoscopic stuff is intriguing, especially that new class of engines.

CHAIRMAN PETRI: But do you want a clinical trial in order to get this GI safety label? Clinical outcome?

DR. LIANG: Yes.

CHAIRMAN PETRI: Okay. Dr. Abramson, what about you?

DR. ABRAMSON: I would think so. To

address Lee's issue, we don't really talk about the context of dealing with everybody. But for the sake of this comment I'm thinking, these are drugs that are going to get registered or approved as a non-steroidal class of drugs. So that's one thing.

So the issue is, are they more -- are they safer from a GI point of view; are they COX-2 selective? And those are two separate issues. If they're safer from a GI toxicity then I think we need the combination of a good endoscopy study and clinical outcomes.

Because I think the endoscopy's important but we don't know yet what it means. And clinical outcomes are so small in number that you know, we might have to study five years to see enough. So I think we need to combine them.

So my own instinct would be to do a 3-month endoscopy study and then a 12-month continuation study looking at clinical outcomes, looking at both. And endoscoping -- and then a 3- to 12-month period I'm not sure what I would recommend, but certainly endoscoping for clinically significant events and possibly some other built-in endoscopy.

CHAIRMAN PETRI: Okay. Dr. Yocum, how do you feel?

DR. YOCUM: Unlike efficacy trials, I think you do need placebo here, and I think that you should link an endoscopy study much as Steve has just talked about, in high risk patients for the outcome. So that I pretty much echo what Steve has just said.

In the clinic, since we're looking at this being a -- I mean, the real issue here is safety. If this is really going to be safe and it's going to be marketed as such, I think we're going to have to demonstrate that safety. And unfortunately, endoscopy trials don't give us that definite link.

CHAIRMAN PETRI: Dr. Katona, do you want to comment?

DR. KATONA: I completely agree that's the $64 question -- that the GI safety is true or not -- and just battling with the question, how long it has to be. If it's a year I think it's reasonable; even if it's 18 months. Anything beyond that we would hold back the drug development so much. So that's my dilemma. So I would like to go for an initial term.

CHAIRMAN PETRI: Dr. Harris?

DR. HARRIS: Well, I believe that the issue -- this is a new class of drugs and from at least the perspective of a labeling issue, I think that we should have clinical trial.

CHAIRMAN PETRI: Thank you. Ms. Malone, from a consumer point of view, does the consumer care whether it's an endoscopy label or whether it's a clinical outcome label?

MS. MALONE: If you're the one undergoing the endoscopy I think you would care.

DR. SIMON: We all remember.

MS. MALONE: One would hope. Unfortunately, you know, I said I -- there should be a way in medical training that the doctor has to get the ailment that -- they can somehow give you the ailment for a week and you have to live through everything that the patient has to go through, and I think you'd be a lot more understanding.

This is very confusing because all I've heard is that with the endoscopy the results don't mean anything anyway. So why are we haggling over this? I mean, obviously there must have been some thought as to why to do the endoscopy; that it must be proving something.

CHAIRMAN PETRI: Well, I think the bottom line is that ulcers are not good.

MS. MALONE: Which we knew to start. My concern is that in anything that's done, I keep hearing, you know, the idea of rescuing the patients.

And that's important. And quite honestly, Dr. Laine, you know, worries me. He does.

I mean, maybe I -- I'm probably -- I hope I'm misinterpreting what he's saying. I mean, that he's expressing himself more as a research person. But that's uppermost. I mean, you have to -- you know, if a problem develops, whether or not it's going to have an effect on the research, that patient has to be addressed.

CHAIRMAN PETRI: But that would happen. I think that's what Dr. Laine has explained. The minute you see an ulcer that patient drops and is treated. So that wouldn't be a concern.

MS. MALONE: Okay, but he wasn't making that clear.

CHAIRMAN PETRI: But the issue more is, do we believe so much that endoscopy is a surrogate for bad GI outcome? That that's enough --

MS. MALONE: No, I --

CHAIRMAN PETRI: If we're going to have a GI-safe label do we really want to be able to tell the consumer, there's this much of a decrease in perforated ulcers and GI bleeds?

MS. MALONE: Yes, and I think you have to be very definite in your parameters when you're

describing it in these measures.

CHAIRMAN PETRI: Dr. Moreland?

DR. MORELAND: I agree with all the comments that have put forth. I would suggest that an endoscopy study would be enough to get it approved but it may not be enough for me to use it, and I'd like to have the clinical outcome to better my judgment.

CHAIRMAN PETRI: Do you want the clinical outcome study to be part of post-marketing? That that will be the arrangement made? In other words, it's not going to be optional?

DR. MORELAND: That would be -- I would agree with that. I can accept that.

CHAIRMAN PETRI: So this should not be optional?

DR. MORELAND: This would not be optional but would be --

CHAIRMAN PETRI: Dr. Fernandez-Madrid?

DR. FERNANDEZ-MADRID: Well, I think the -- I would agree with Dr. Moreland that the endoscopy study is the best surrogate that we have. But I think we discussed why this is not optimum and really, it does not -- it is not equivalent to major outcomes.

So I am for everything that has been said, but it is not predictive of a major outcome. I would

mandate a clinical study in the post-marketing period, definitely. I would not leave it optional.

And I think this is the most important piece of data that the public, the physicians and the drug companies would need. That is, we fill our mouth saying that every year 1500 patients die in Britain, that 7,000 patients die here for massive GI bleeding or perforation.

We will not know these from endoscopy data. We will not be able to say anything about it. So I think we do need the clinical outcome studies.

CHAIRMAN PETRI: Dr. Brandt.

DR. BRANDT: Yes, as we went around somebody make a comment about a one year study and a placebo-controlled study. With regard to osteoarthritis, there's only one effort and a long-term placebo-controlled, NSAID trial, and the results are relevant.

That was a 2-year study done in Bristol with dioclofenac versus dummy dioclofenac, with about 50 percent dropout rate because of lack of efficacy or side effects. And that was with rescue perisenamal. So if you're thinking of big numbers, now double them.

CHAIRMAN PETRI: Comment from the audience.

DR. KEMMY: Kemmy; I'm from Seattle, too. You know, I think endoscopy studies are interesting and I think should be done, but they don't do anything about looking at ulcer healing; they don't look at anywhere beyond the duodenum.

I think that although this appears to be a new class of drugs it's still an NSAID; it still inhibits prostaglandin and synthesis. And I don't think we have really enough information yet to know, you know, what the relative importances of COX-1 and COX-2 are in the GI tract.

I mean, it concerns me about healing. We think that ulcers come and go in people taking NSAIDs; there's lot of data bout that. And we really wouldn't get a handle on that by just doing a simple endoscopy study where patients drop out if they have an ulcer. So although endoscopy studies are interesting I would really strongly favor an outcome study.

CHAIRMAN PETRI: Thank you. Dr. Simon.

DR. SIMON: After listening to the discussion and I know it's going to --

CHAIRMAN PETRI: Here you go.

DR. SIMON: -- rock everybody to their core, I think that that comment is a very important one because in fact, I'm coming at this from the

belief that this is not a non-steroidal. Not that you think that I think that.

Clearly to me, we should be thinking about this in a very different way, and as a result, because we're really interested in knowing about bleeding that can't be accessible unless we have an ilioscope or even something longer to be able to determine whether there's damage far down in the gut under these circumstances, then the fact, because I know the pre-clinical data about these drugs -- which I think are very important for the way we should be thinking about how to design the trials here -- I'm not sure that endoscopy will tell us as much as a clinical outcomes trial is going to tell us.

Particularly as it relates to what these drugs really do because they are not non-steroidals as we think of them. So therefore I don't think we should be thinking of them as a traditional registration for non-steroidals, and just immediately apply a pat answer of endoscopy to find out what their toxicity is.

If the question is, what are the biologic effects of these drugs and how safe are they, in general -- I mean, for antibiotics I'm not entirely sure I'd want to endoscope a new antibiotic. And I'm

not entirely sure I understand why endoscopy is necessary in this particular trial set. And I do believe that a clinical outcomes trial would be very important. And so maybe I've changed it a little bit.

CHAIRMAN PETRI: Post-marketing?

DR. SIMON: Sorry?

CHAIRMAN PETRI: Post-marketing?

DR. SIMON: No.

CHAIRMAN PETRI: You're going to require it for registration of the drug?

DR. SIMON: I've now gotten to the point where I'd be more interested in that.

CHAIRMAN PETRI: A comment from the audience.

DR. GOLDSTEIN: Jay Goldstein, University of Illinois. I question the issue about the duration of one of these outcome trials. Understanding the benefit of them is -- 18 months I heard; 12 months; six months. I believe that six months is more than reasonable given the fact that we have baseline endoscopy data that would support the lower incidence of ulcers or supporting that kind of concept.

Though after the 3-month trials of endoscopy trials or 12-month trials looking at endoscopic rates, I think that outcome studies lasting

six months would be more than adequate.

CHAIRMAN PETRI: I think your point is well taken. There's no one on this committee who has done a power analysis. I think that's really going to be essential in terms of both numbers and length of study. So I don't think anyone here wants to determine the length of that clinical outcome study.

Yes, Dr. Johnson?

DR. JOHNSON: Ken Johnson from the FDA. Yes, I would like to make a comment in that regard. Because really the length and the patient requirement -- assuming you've got a fixed hit rate over the duration of your trial -- vary inversely.

So if you need 10,000 patients for six months you could do it in 5,000 patients for a year. So there's a bit of a handle on this and the traditional two to four percent data that was indicated this morning came from a whole series of NDA-controlled data, determinations of patients in non-steroidal trials who dropped out because of some variant of a GI symptom.

And there was a lot of difficulty in assuring that there was sort of balanced ascertainment of working up these problems and so on and so forth. But there was pretty much of a uniformity across all

the non-steroidal NDAs that existed at that time in the two to four range per year.

So you could power your trial very simply. I mean, the tough issue is to describe a clinically compelling endpoint that still has high enough of a hit rate. And if you can do that in that two to four percent range -- and then you're talking about 5,000 or 10,000 patients over six to 12 months.

DR. LAINE: It's a real problem in terms of that two to four percent because if you only look at really significant things like perforation bleeding it's well under two percent, you know, as we showed. It could be one percent, it could be point-one percent, and then when you start powering it gets incredible.

On the other hand, if you endoscope everybody who has dyspepsia you'll find ten percent or 12 percent or 15 percent that have ulcers and then we're really into clinically-significant lesions. So I think deciding that is a really key point because it dramatically alters what your assumptions are and therefore what your power is.

CHAIRMAN PETRI: Dr. Moreland.

DR. MORELAND: I have a question as to the outcomes trial, as whether you're designing this in a

group of RA patients or a group of OA patients. Specifically, if it's a group of OA patients is it ethical to give them continuous, current standard, non-steroidals for a year knowing the flexibility and the disease activity?

CHAIRMAN PETRI: Well, let me ask Dr. Brandt whether he would feel comfortable with NSAIDs for a year in OA.

DR. BRANDT: I think there would be a considerable dropout rate with an effort to do that. There's a study from Canada by Shoals a couple of years ago looking at knee OA patients who were started on an NSAID -- any NSAID.

Only 15 percent were on the same NSAID at the end of the year because of either lack of efficacy or lack of side effects. So there's an escape valve, in a sense. It's a very tough thing to do for both efficacy and side effects reasons.

CHAIRMAN PETRI: Comment from the audience.

DR. LYMAN: Thomas Lyman. One question I guess is whether endoscopy studies were really all created equal. For example, one thing that was mentioned is whether one would look at an endoscopy study that was designed to show equivalence to placebo

in the same way one would look at all others.

What I'm saying is, if one designed an endoscopy study and showed equivalence to placebo within some reasonable bound, one still would want an outcome study in the face of that.

CHAIRMAN PETRI: I think the answer is yes, but there is not consensus in the committee about whether it should be required for registration of the drug or whether it should be post-marketing. I think it might be helpful just to have a show of hands here so we can see how the committee is divided.

If I could see a show of hands first of people who believe that the clinical outcome studies should be required for registration of the drug?

DR. LAINE: Are you saying registration meaning approval, or approval with the safety off?

CHAIRMAN PETRI: GI label is given, the drug is approved. Show of hands? You would get the GI safety label based on the endoscopy findings. But it would be also required for registration, that you have your clinical outcome study. For both.

DR. LIANG: So you couldn't actually get approval of the drug until you had the clinical outcome study?

CHAIRMAN PETRI: We have two choices: you

have to have the clinical outcome study for approval, or it's post-marketing. Those are the two choices I'm going to give you. I could give you three, but I'll make it easy with two. Steve?

DR. ABRAMSON: There's a third choice.

CHAIRMAN PETRI: I knew you were going to do that.

DR. ABRAMSON: Because will it be acceptable for these drugs to be registered as NSAIDS with the same class label without any mandate for endoscopy or outcome studies. We should have a vote on that as well.

CHAIRMAN PETRI: Well, why don't we do this vote first and then I'll let you pose your question next?

DR. SIMON: That's -- I can't vote on that because I don't -- I have to assume that we're deciding if this is then, a non-steroidal. If this is then a way that we're going to handle it, that's very different than if we're going to deal with it when it biologically behaves. Which would require an entirely different discussion.

So that has to be defined up-front, I think. So are we saying that this is registered as a non-steroidal?

CHAIRMAN PETRI: Well, let's go back to Dr. Weintraub.

DR. WEINTRAUB: That is a question; it's a very important question. The thing is that we could -- in our thinking right now we could say that an outcome study which is reported after -- you know, post-marketing -- would probably be presented to the world with the current GI labeling, unless the clinical trials before that were so astonishing and so overwhelming.

And I don't think that they can be because what would be the type of study that was done would be an endoscopy study. So we are faced with the necessity for maintaining the non-steroidal, anti-inflammatory drug template.

Okay, now that's if the clinical outcome study is delayed until after approval, and then we can go back in and change -- we can change anything. Now, when the study however, is presented before approval we have more options.

You know, right now, whether Dr. Simon believes that these drugs are different or the same, we have to start somewhere, and where we're going to start is with the current GI labeling.

DR. ABRAMSON: So just to follow up, if

company *X* had this COX-2 inhibitor and wanted to come forward for approval as an NSAID with no specialty claims, do you see anything right now that would make you uncomfortable about giving it an NSAID class label?

DR. WEINTRAUB: You know, it's not a question of my comfort or not. We would still have to -- until the NSAID template was overturned, we would have to use that.

DR. LAINE: But I thought the question with the endoscopic studies would be if they did an endoscopic study and showed there were less endoscopic ulcers, they could still say there were less endoscopic ulcers but they wouldn't say there's less -- the actual safety issue wouldn't be taken away. So it seems to me that's one of the --

DR. WEINTRAUB: Right. As I said, you can always get the clinical trials or clinical studies -- I don't remember what it's called -- section of the label changed. And you know, I've said that many times; that the hurdle -- the higher hurdle, the higher barrier, whatever you want to say -- is the -- template -- the GI warning. But you could get your material into the label and into the clinical trials.

DR. LAINE: I understand, because it

sounds like the question then is a little different for me. It --

CHAIRMAN PETRI: The question is actually quite simple. It's clinical outcome required pre-marketing, or post-marketing.

DR. LAINE: See, I actually think -- I think it relates to the claim, though, and that's my problem I'm having, I think.

CHAIRMAN PETRI: Well, I think what Dr. Weintraub is bringing up is, there are different hurdles in a GI safety claim. So we would certainly allow that first hurdle based on endoscopy.

DR. LAINE: So the question we're asking here --

CHAIRMAN PETRI: This is the second hurdle, the clinical outcome hurdle.

DR. LAINE: So what you're asking is --

CHAIRMAN PETRI: That's a higher claim.

DR. LAINE: Just for me to get straight in my mind, you're asking is that they showed endoscopically it was better but they had not had the clinical -- you're asking in addition, before they can get the safety claim off -- in other words, before they can say they're safer than a standard NSAID, whether or not to require a clinical outcome study.

Is that what you're saying?

CHAIRMAN PETRI: Right. Yes.

DR. LAINE: Okay. Sorry, I'm just --

CHAIRMAN PETRI: So again, if I could just summarize it very quickly: pre-marketing or post-marketing. So I think everyone here is agreed we want to see that clinical outcome data; that was unanimous. The question is, when.

So if I could see a show of hands for those who believe that it should be available pre-marketing? And those who would allow it to be post-marketing? Are there any who did not vote? Okay. I didn't think it was everyone.

Yes, Kathleen Reedy is commenting that it looked reasonably even, so there's not a consensus here.

Let me ask the FDA representatives if there's anything specifically that they are concerned about?

DR. WEINTRAUB: Really in truth, I mean, whatever the committee decides, it would be helpful to us, it would be helpful to the industry as well. But an individual company will make its own decision on this particular issue. It can -- it absolutely can make its own decision.

CHAIRMAN PETRI: Okay, Dr. Simon first and then Dr. Laine.

DR. SIMON: So I guess that what we just said is that for registration now as a non-steroidal, that it would be adequate to demonstrate that they were safe by endoscopy, but if they wanted to have a superiority claim for GI toxicity, then the expectation would be of a clinical outcomes trial to prove that. Is that kind of what we've just kind of given you evidence of?

CHAIRMAN PETRI: Yes.

DR. LAINE: But instead of toxicity we really will say clinical outcomes, because ulcers may be toxicity but not clinical --

DR. SIMON: Well, in an evidence-based parlance then, that the clinical outcomes are fewer or zero, in that lexicon, as opposed to the traditional non-steroidal. Is that how you read that?

DR. WEINTRAUB: Yes. The thing is, the -- I mean, that represents a change in some of our thinking on the inside. Inside, you know, from the black box, we look out to the world and we see things a little differently.

But our own thinking has evolved over many months of worrying about what studies should be done,

when they should be done -- just as you were just going over. Initially, we were concerned about all endoscopy. And the endoscopy perhaps, has changed over, much as you have done, have changed, to more thinking about the clinical outcome study.

But we're still worried about how one measures the fact that this is no different than placebo and how one accepts the fact that it's no different from placebo. We're worried about that.

DR. SIMON: Isn't no difference in placebo being no different than placebo?

CHAIRMAN PETRI: Well, it's an equivalence, though.

DR. SIMON: I'm not sure I follow that.

CHAIRMAN PETRI: Well, equivalence trials are so hard to power.

DR. SIMON: No, I understand the powering issue. That's what you mean by that, is the powering issue?

DR. WEINTRAUB: Yes.

DR. SIMON: Okay.

CHAIRMAN PETRI: Dr. Abramson.

DR. ABRAMSON: I do apologize for being dense on this, but I'm not sure what we voted on. Do you take that to mean that for approval as an NSAID

class now -- either pre-marketing or post-marketing -- GI safety studies had to be demonstrated for approval for NSAID class labels?

DR. WEINTRAUB: No, they don't have to be demonstrated for approval. If you did an endoscopy study we could put it in the clinical trial section. In fact, even if you did many kinds of studies -- they could get in the clinical trial section.

Changing the gastric and duodenal template is a higher barrier, and we're saying that that would require a clinical outcomes study. I don't know of what type. We're hoping you'll discuss what type that will be.

DR. ABRAMSON: If company *X* didn't want -- COX-2 inhibitors clearly are directed to improve GI toxicity, but if a company *X* said look, I'm not going to go for that bar. You're going to set the bar too high; I just want to bring this COX-2 inhibitor onto the market with no endoscopy studies, would you -- and no change of label, just an NSAID --

DR. WEINTRAUB: You say no endoscopy studies? I'm sorry.

DR. ABRAMSON: I've got a drug, I've decided I want to bring it to market and call it an NSAID and worry about convincing people that it's

safer in other venues because I haven't liked the bar that the FDA has set for GI toxicity, would you then approve these class of drugs as an NSAID --

DR. WEINTRAUB: Of course, if they have the safety and effectiveness data --

DR. ABRAMSON: That's all.

DR. WEINTRAUB: -- that's it. That's all we would require.

CHAIRMAN PETRI: Now, I think we'll be answering Dr. Weintraub's question if we go on to number 2 which is, what kinds of endpoints should be considered for approved GI safety?

And just to review our three. Dyspepsia, we've been told that there are some instruments available that I assume are valid and reliable.

DR. LAINE: Not necessarily for NSAIDs but for dyspepsia. You probably, you might argue have to do -- I'm sure Tom Simon would -- have to develop a new instrument for NSAID dyspepsia, one could argue.

CHAIRMAN PETRI: And then let me ask Dr. Laine specifically, the endpoint --

DR. LIANG: That's what Tom Simon is going to say.

CHAIRMAN PETRI: The endpoint on the endoscopy study is going to be --

DR. LAINE: Ulcer.

CHAIRMAN PETRI: -- ulcer. Three millimeter or five millimeter?

DR. LAINE: Well, again I think -- I think three millimeter only give -- I hate to say tradition -- but if every other study has been three millimeter the question is, is it fair? I mean, that's really what Lee was saying earlier.

Some of these things we would perhaps like to change and the question is, is it fair to change them when companies compare numbers and you know, when they market things, is it fair to have a company now all of a sudden have to have a five millimeter ulcer?

I think the depth is the real key. I think it's a problem, but I would probably use three millimeter right now. If a company wanted to go larger they could.

CHAIRMAN PETRI: It bothers me a little bit about what's fair. Why don't we go after what's the truth? Because if five millimeters is what you think is most predictive of the poor GI outcomes, why wouldn't we gravitate towards the truth?

DR. LAINE: Well, two things. Number one, nobody knows that for sure, and I would suggest that depth is of equal importance. And I think -- I mean,

I think we have to be somewhat reasonable in this -- I mean, I agree we have reasonable.

But then I think you would want to go back and look at all the other people's five millimeters and re-label them, because otherwise five millimeters may be less common, so all of a sudden you're going to have very markedly different numbers in the labeling, and I can't believe that that's not important. Maybe others disagree with that.

CHAIRMAN PETRI: Dr. Simon.

DR. T. SIMON: Just wanted to back up to the dyspepsia comment and confirm Loren's impression is correct. There isn't a validated dyspepsia questionnaire that one could use to measure it in the context of NSAID.

CHAIRMAN PETRI: All right. Well there's an avenue for work. Dr. Brandt.

DR. BRANDT: Question: what proportion of five millimeter erosions do not have perceptible depth?

DR. LAINE: I just don't know. I mean the point is that it's felt to be rare, and really what -- the reason it's largely done is that it's said that endoscopists really don't know for sure. So if it is five millimeters it's more likely to have depth and

more likely to be a true ulcer histologically.

That stated, I don't know that that's been absolutely, you know, confirmed, and that's why people sometimes use five millimeter. I think all this stuff though, is very, very iffy. And if you had a three millimeter ulcer that was quite deep, that would probably be worse than a five millimeter that was very shallow.

So I think it's just very difficult to know. This is all just picking it out of the air. I think people sometimes use five just to be more sure that it's an ulcer and not an erosion.

We have to remember when you're talking about these studies, there's an economic incentive to the investigator to find an ulcer, because if he finds an ulcer he enters his patient, he or she gets lots of money for that endoscopy, etc. So we have to keep that in mind. That's another reason to consider five.

I think everybody feels more comfortable with five, but people keep using three because that's what's always been done.

CHAIRMAN PETRI: Comments on the three versus five? Dr. Katona?

DR. KATONA: Why can't we just keep a track of measure than three and four and five? But I

think I agree that until now we always took it from three; I don't think that that's reasonable to change it.

CHAIRMAN PETRI: Dr. Fernandez-Madrid.

DR. FERNANDEZ-MADRID: I think I would like to address a question a few of you raised on fairness. I don't think that we should repeat what we have done in the past if it is wrong. That is, we have trials for non-steroidals for the last 15 years, and thinking changes, we simply improve, we go down some area, but I think the thought changes.

So if there is something that is better at the present time we should use it in spite of the fact that we have done differently in the past.

DR. LAINE: I guess I would agree with that. I guess when we don't know for sure that there's clear evidence to distinguish the two and we have that other issue there -- that "fairness" issue -- I guess I'm not sure that I would go about changing this unless I had -- I mean, obviously if I had very good evidence that five fully predicted and three didn't, then I would say, absolutely you're right and we should just ignore what's been done in the past. I don't think we have that evidence so that was why I was suggesting staying with three.

CHAIRMAN PETRI: Okay, so I think the consensus there is, three millimeters until there's further data. And the next thing we need a definition would be what are going to be our clinical outcome variables.

And Dr. Laine, you were telling us in the mucosa trial they were lumped -- bleed per, gastric outlet, all lumped.

DR. LAINE: Well, they actually collected them separately and they had a very complicated -- Dr. Silverstein and others can speak to that -- but they had a very complicated list of different kind of levels -- I think ten different levels of complications.

And then they actually lumped them together, and when they lumped them together they did show -- you know, all upper GI complications due to ulcers or erosions or -- they did show significance.

I think you just have to define it a priori. I might have defined it differently than Dr. Silverstein but you know, I think as long as you get a group of people together and define something that's reasonable to that group, that's how I would do it.

I'm not sure --

CHAIRMAN PETRI: Well, if we assume that

this is all a continuum, is there anything incorrect about lumping them?

DR. LAINE: No, I think that's acceptable if you just define -- I think you just need to define it a priori, is the point. You can't say afterwards I'm going to lump everything. You need to say, I'm going to look at all complications including bleeding and perforation, for example. I think that's fine. Just define it a priori rather than -- and don't define it after-the-fact.

CHAIRMAN PETRI: Let me ask the committee for their impression. Are you willing to lump these bad GI outcomes? Do you think any one of them should be looked at separately? Dr. Brandt?

DR. BRANDT: I think there's some virtue to splitting. I think one of the points about the ten or 11 scaled mucosa list was that it included some ambiguities. They weren't all definite and in descending order. Some of those were a reflection of the fact that the data didn't permit a definite decision, unambiguous bleed.

CHAIRMAN PETRI: Also, our sample size is going to go way up here if we split. Dr. Silverstein, you wanted to comment?

DR. SILVERSTEIN: Thank you. Just a

comment about what happened. I agree completely with what Loren said. I think Loren just said it; that you really want to define going into it what you're going to call success and not success. Because otherwise it's going through the data and then making it work for what you want. I think it's very important to say, this is what we consider to be a bad outcome.

Part of the problem, when the FDA made its warning in 1988 of two to four percent per year, was it included the symptomatic ulcer along with a true ulcer complication. And then it was difficult for people planning a trial who didn't want to include symptomatic ulcer as a complication, to know, well what was the real number?

In other words, two to four percent to the year was a symptomatic ulcer or a complicated ulcer with a bleeding or a perforation. Well, how much of each? And so we didn't have that number in terms of knowing how to power the trial.

Now what happened -- we should learn from what happened -- I mean, what happened was, with 8800 patients we found in six months, one percent of people on NSAIDs and placebo had one of these complications as we defined it, and if they were on Misoprostol as you heard me say this morning, it was about half of

that.

And then that achieves -- just achieves statistical significance. So it gives you some idea going forward about what kind of numbers are going to be required.

And certainly, Ken's point is well taken that having learned from that, the importance of a 3-person extramural group to review this, and the importance of going to the investigators in a prospective way and saying, you've got to get the data for us. We're not going to sit here and look at, you know, blank forms and try to make a decision. You've got to give us the data.

And then you sit -- and it's very difficult. You know, the patient vomits blood. Is that a bleed or not? Well, somebody would say, of course it's a bleed, you know, she vomited blood. Somebody else might say no, she had a bad nosebleed and she swallowed the blood and them vomited it.

So the more you get into this the more you realize it's not that simple to make these definitions. So what you try to do and what we're currently doing, is to make reasonable definitions that you can stick to and then say, if the person has this we're going to say that's a significant

complication within the category of GI bleeding.

Perforation's easy because we require freer in the abdomen, surgical closure, you know, we make it pretty clear. Probably the most difficult is obstruction which is a somewhat subjective diagnosis. But within bleeding you have to be flexible enough with experience. You have to be experienced enough in management in bleeders to know they're not always so easy.

Now, what you do about the people who are bleeding but they're clearly not having an upper GI bleed, is clearly track that data at a minimum. You would keep track of how many people have that. But in the mucosa trial most of the complications we saw were in fact, upper GI, ulcer-related, bleeding, and perforation.

CHAIRMAN PETRI: Let me pin you down. Are you happy lumping bleed, perf, gastric outlet obstruction?

DR. SILVERSTEIN: Yes. Well, I think what you're saying is, an adverse GI outcome is a perforation, a bleeder, an obstruction. And you'll lump them.

CHAIRMAN PETRI: Yes, because obviously --

DR. SILVERSTEIN: And you say that's what

we're after --

CHAIRMAN PETRI: -- we won't require as much of a sample size.

DR. SILVERSTEIN: Right, right. And that was one percent in six months, two percent in a year -- which is pretty much consistent with what the FDA said, you know, ten years ago. It's pretty consistent. And then within that you can subcategorize that.

You can look at bleed, perforation, and obstruction as subcategories. But you go into it as saying, if it fits into these -- any one of these three things, that's an adverse outcome. Otherwise, you're going to need 30,000 people.

DR. LAINE: The problem is, if you don't lump it's almost impossible -- it becomes almost impossible -- certainly for perforation, micro-bleeding -- the numbers required are so high that it really becomes difficult.

DR. SILVERSTEIN: As long as you get --

DR. LAINE: It's pretty difficult anyway.

DR. SILVERSTEIN: Right, as long as you get agreement that everybody would say, this is the stuff -- this is what worries us about this class of compounds -- is any one of these things. That's what

we don't want have happen.

So for example, if you said nausea or vomiting, I wouldn't include that. I would say, it's too complicated; there are too many other things it could be. Whereas, GI bleeding I would definitely include in that.

CHAIRMAN PETRI: Thank you. Dr. Johnson?

DR. JOHNSON: In answer to the comment about the complexity, I think all the company gastroenterologists have to get on a phone call and sort of work this out for us.

I had a question for a statistician. I hope I can get a response. If you had to lump to get sample size reasonable, okay -- which I think you probably do -- and you've got an outcome which is a bad outcome, what would happen if you actually had a 3-way outcome.

You know, clearly sailed through without a problem, some sort of ambiguous middle category, and a third category of clear failures. Would having a 3-way division make your sample size requirements worse or better or indeterminate?

CHAIRMAN PETRI: Is Dr. Patrician here?

DR. PATRICIAN: Ken, you earlier asked me a hard question. We have done some cardiovascular

trials where we studied the composite endpoint. For example, time to event, MI, stroke, death, those kinds of things.

So I think this is a very tricky endpoint. You may have the -- it relates to the clinical effect from where the clinical effect is coming -- which endpoint is coming -- so the clinical endpoint which is really dominating the effect, that will play a role in driving the result.

So once you get an effectiveness result for the composite endpoint -- it's like in statistics, you got all the result and then you have the responsibility to find out which endpoint is really contributing to the part.

There are ways to do it. You have to have calculate the effect size for each and then work out the statistical methods to do that.

CHAIRMAN PETRI: Dr. Laine.

DR. LAINE: Well, I would just say, I'm not sure we would want to do that. I mean, I'm sure clinically it's meaningful. I think you just define what's bad and what's not bad for your safety issue and just kind of break it down. I'm not sure why we would want to complicate it.

CHAIRMAN PETRI: Dr. Moreland.

DR. MORELAND: I don't want to get off-track but I want to just throw out something. Let's assume the hypothesis that COX-2 inhibitors are completely GI safe. And the endoscopy studies proved that; that there are very few if any, lesions.

What are the ethics then, of putting someone into this post-marketing study with the current non-steroidals?

CHAIRMAN PETRI: We're still looking at for small and large intestinal problems, right? We can still have --

DR. MORELAND: Let's assume though, that the endoscopy studies show that there are zero patients in the COX-2 inhibitors. Is it ethical then, to put someone on a current non-steroidal in this clinical trial?

CHAIRMAN PETRI: Any comments?

DR. LAINE: That was the point that Dr. Simon -- the other one -- raised earlier and I think it's a very good point. The only point is, if there are no ulcers than obviously there can't be any upper GI complications. So I think the point he raised earlier is a very reasonable one, and the only issue is, could you then do a separate safety issue looking at only small and large intestinal tract lesions?

And certainly to go back to what he said earlier, at that point perhaps, it's not -- it would be interesting, certainly, as he mentioned, if you did some of these other marker studies and showed there was absolutely zero difference, it would be suggested that there wasn't even minor, large intestinal or small intestinal disease as well.

And all of that together might start making you, you know, lower -- or you know, not require quite as much information, I would agree.

CHAIRMAN PETRI: Dr. Abramson.

DR. ABRAMSON: I think Larry's point is well-taken and logically it would seem if there are zero ulcers. But I don't think that we can go from a situation where we say ulcers and endoscopy are not predictive and then say that if you don't have an ulcer you're not going to get a clinically important ulcer.

And part of the -- one question I had earlier that pertains to this is that, if you have 30 percent of ulcers at three months and six months and one year, are they the same 30 percent? Because if they're not then that answers the question, I think.

DR. SIMON: Nobody knows that. Nobody's been able to go in and label them and then go back

each time --

DR. LAINE: There are studies that show them coming and going.

DR. SIMON: The same person; that's what I mean.

DR. ABRAMSON: So if 30 percent have it at three months and then, you know, do we know?

DR. LAINE: There are some studies where people have shown that they do come and go.

DR. ABRAMSON: New people, but different people get ulcers at six months from people who get ulcers at two or three months.

DR. LAINE: Oh, actually, in those studies, no, it's accumulative incidence, so they're out of the study at the moment at which they get the ulcer.

DR. ABRAMSON: But then there are -- so it's new patients that come on with ulcers after this --

DR. LAINE: No, I mean, they're out of the study. It's a smaller number who are still remaining. You know, at one month if ten percent have an ulcer, now they're gone.

DR. ABRAMSON: New people are getting ulcers, so the absence of ulcers at three months

doesn't say you're not going to have ulcers at six or ten months?

DR. LAINE: Correct.

DR. ABRAMSON: In those people who remain in the study?

DR. LAINE: Those studies did show a flattening off, so you have a -- you know, presumably the higher risk people are taken out early and then the rest of the people left in, not too many of them are going to get -- not as many of them are going to get an ulcer.

CHAIRMAN PETRI: So I think we've done a reasonable job of defining what we want for clinical outcomes with that one caveat --

DR. WITTER: Excuse me, Michelle.

CHAIRMAN PETRI: Yes?

DR. WITTER: Could we actually pick up on Dr. Silverstein's comments a bit more about whether there's some kind of a consensus for outcomes in clinically relevant -- clinically relevant outcomes in terms of things like perforations, bleeds, obstruction? Could we have some more discussion about that? Or, do I take it from your comments that everyone is satisfied with those kinds of outcomes in a trial?

CHAIRMAN PETRI: Well, let me specifically ask. I had asked about lumping these bad outcomes because it would allow a study to be done with a smaller sample size. It seemed to fit pathophysiologically because we thought it was a continuum. Dr. Simon?

DR. SIMON: I think that perforation obstruction doesn't really deal with the various different kinds of bleeding, and then the question is, what do you mean by bleeding? Is that just positive -- is evidence of melena or is that hematochesia, is that bright red blood per rectum, or is that vomiting up blood?

Is there going to be required an endoscopy associated with that, define what that is as opposed to a nasal bleed versus something else? Although of course, we won't have nasal bleeds because there's no platelet effects in this drug, but nonetheless, I think that this is a real problem.

So I think bleeding needs to be defined in all the parameters -- all the permutations, excuse me -- of potentially what bleeding means. But to be clearly defined.

DR. LAINE: I think that actually is very doable, I mean, having done it in studies previously.

And basically you just have a few people get together and decide. I think that that's not the tough thing.

Frankly, I think obstruction bleeding and perforation are key, and obstruction as Fred said, may be a little harder because there are different levels of obstruction. At least with bleeding you can define in terms of vital sign changes, hematocrit changes, things like that. But obstruction, it's not perhaps quite as easy.

The fourth thing that I would raise for the committee is, do you even want to get into pain; i.e., the type of severe pain which incapacitates the patient which is obviously a small proportion, but is that worth getting into or not?

I mean, to me that's the hardest question about the true GI complication because that's very hard -- you know, it's hard to define exactly where on the continuum you will endoscope a patient; what will be the thing that will trigger you to endoscope the patient. But I think that's something that would be important to decide whether you want to consider that or just exclude it and only have those other complications.

CHAIRMAN PETRI: Dr. Silverstein?

DR. SILVERSTEIN: Well, a lot of what I

know about GI bleeding I actually learned from Loren, so we're going to agree about a lot of this. But Lee, you're absolutely right that, you know, you really have to be careful because when you really do this -- like, you know, those of us who sat and actually looked at these patient folders -- and melena by itself it tough. You know, she said she had black stool but now it's brown. You know, well, did she bleed or not?

And in hematocrit change, you have a person on NSAIDs who drops their hematocrit and has hemocult positive stool. Odds are, it's a colon neoplasm that's bleeding. So that's what I was talking about. I wasn't being glib when I said these are not easy clinical diagnoses to make.

That's why I have suggested that it's good to have a panel of people to look at each case. I do however, agree with Loren that if you look at an ulcer and you see an adherent clot or there's blood coming out of the ulcer, that's one of these lesions I'm talking about.

If you have somebody vomit blood and you document the presence of a lesion, that's what I'm talking about. So what we came up with was not really a hodge-podge. It was more saying, if you see a -- we

require a lesion, so either endoscopic or x-ray.

And you might say, how could you possibly do x-ray? Well, some of these 85-year-old people just aren't going to be endoscoped; they won't let you. Most of them will. So you have to have a lesion and then you have to have other factors to modify it. Just having an ulcer doesn't make it into that category.

But hemotemesis with an ulcer does. And you know, as well, changes in vital signs or changes in hematocrits. So I think it's an important issue for the agency to deal with -- how do you define these things?

DR. WITTER: And just picking up on your comment of a panel, would you like to see so that these endpoints are common between various companies that are doing these kinds of trials, that the same kind of outcomes are utilized in these trials? Would that be of interest?

DR. SILVERSTEIN: Yes, I think so, for the same reason that we were talking about not changing the three millimeter to five millimeter. I think they should make sense. I think if you get a bunch of gastroenterologists together they're not all going to agree about every part of it, but basically they're

going to say yes, these are reasonable parameters for this kind of a study.

And so I would say if you can come to some consensus it's going to make it a heck of a lot easier to interpret the data from one and another study.

DR. WITTER: Do you have a suggestion how we can go about getting such a consensus?

DR. SILVERSTEIN: Well, you can start with what we did in the mucosa trial because that's the only data to my knowledge that's been published, and it had, you know, issues with the trial. But on the other hand, it's the only data. I mean, thousands of hours went into it.

Start with that, convene a group of people, you know, like Loren and Dean Jensen, and Mike, and some other people who are experts in bleeding, and see how everybody feels about it and come to a consensus.

But I don't think -- as Loren said -- I don't think it's rocket science. I think it's more a question of clinical experience and saying, you know, just vomiting up blood by itself, it would seem -- when I was an intern that sounded like an upper GI bleed -- but when you have more experience it can be more complicated than that.

But I do agree with you that if you can come to some kind of consensus it will make interpretation going forward an easier issue.

CHAIRMAN PETRI: Let me ask you to vote on the two things. Would you include pain?

DR. SILVERSTEIN: I would not include pain because in fact -- one comment about symptoms in general. There have been some very nice studies that have shown that patients on NSAIDs who have symptoms don't have a lot of damage, necessarily to their stomach and duodenum. And patients with ulcers don't necessarily have symptoms. And then there was --

CHAIRMAN PETRI: So you would also not include symptomatic ulcers?

DR. SILVERSTEIN: So I would not include symptoms because I think, as Loren said, that's probably the most difficult of all these things to adjudicate. And there was a classical study by Armstrong, Blower, and Gutton about 1985 that looked at -- take patients who are on NSAIDs and patients who are not on NSAIDs who present with a life-threatening complication.

And it turned out the people on NSAIDs had a lower incidence of antecedent symptoms than the people who were not on NSAIDs. So the question was

whether the NSAIDs had an analgesic effect that it was masking the symptoms. But the whole area of symptoms is extremely complex, and I personally would not include it because I think it's going to be the softest endpoint of the bunch.

CHAIRMAN PETRI: Thank you. Dr. Singh.

DR. SINGH: Just taking what Dr. Silverstein said, taking that a little bit further. You know, when you would convene this consensus, one of the things that I think should also go into it is that, how much should one look for the evidence?

That you know, if you have a certain presenting symptom, for example, do you then do endoscopies on those patients? Would you -- if you have melena, what do you do about it? So not only should there be a definition of what constitutes and endpoint, put what do you need to do to prove certain things that would lead toward an endpoint?

It's one thing going in after the fact that after a clinical trial is done and then looking at the case reports and seeing which one match your criteria or not. But I suggest that you should probably set up well in advance what level of investigation you have to do to get to that endpoint.

CHAIRMAN PETRI: I think that is very much

appropros to what Dr. Witter has suggested; that there needs to be a consensus and that consensus will then be carried through every trial. Dr. Palmer, do you have comments?

DR. SINGH: And then that consensus should be like put in the public domain, because we know that the different drug companies -- all these companies that have NSAIDs have their own committees and each one of them is developing their own consensus.

But I say should have something that's then put and published in the public domain, that that's something that everybody can go by. And there's then one set of rules that all people follow and not different sets for different companies.

CHAIRMAN PETRI: Your point is well taken. Dr. Palmer?

DR. PALMER: I'm following right along in complete agreement with the last few speakers. I think that we need a consensus and I personally favor the kind of approach that Dr. Silverstein pioneered in the mucosa study as a way to look at and display the data, and if necessary, lump them so that you can have reasonable sample sizes.

But there is one other approach that I think the committee ought to at least think of and

it's something I thought a lot about and I'm not sure that I'm in favor of it. But some people have used -- are under the assumption that any outcome study of the kind we're talking about, it's going to be a very large study. It approaches the nature of a large, simplified, clinical trial, if you will.

In which cases you're using the size of the trial to get rid of a lot of uncertainties that would be very important in a smaller trial. So some people for example, have recommended simply using the regulatory definition of serious to define the clinical events of interest.

And recognizing that there will be some inaccuracies in that but they will randomize and distribute equally among the large groups. And that would -- it's a much simpler way of looking at it, although subject to certain inaccuracies.

CHAIRMAN PETRI: Any other comments? Let me ask Dr. Witter if he's happy with the discussion? Satisfied with the discussion.

AUDIENCE PARTICIPANT: May I make one last comment? It's a very important point that Dr. Palmer raises. In fact -- but I see it slightly differently. When you have a large trial like the mucosa trial, we looked very carefully, what are the differences

between the groups? Because the differences you're looking at are small.

So if you found out, oh my -- you know, 75 percent smokers in one group and ten percent in the other group, or you know, steroids in one group and not in the other group. But when you put together a study with 4500 or 4,000 people in each group, they balance extremely well.

So one of the nice things about that is, you don't have to do sub-randomization by category, whereas in the smaller trial you have to be very careful about that. For example, with H. Pylori or a variety of other factors.

So when you get a big trial with two large groups, I don't think you have to be as worried about being sure that male/female, the racial distribution is exactly the same. It does it by virtue of the numbers.

CHAIRMAN PETRI: Thank you. Dr. Witter, any comments?

DR. WITTER: I was just -- any discussion about -- this morning I think I heard in terms of endoscopic outcomes there's a certain hierarchy that people are comfortable with. For example, petechia are not the same category as an ulcer. Any discussion

regarding clinical outcomes, the same kind of -- can they be re-arranged in any kind of a similar hierarchy?

DR. LAINE: I personally wouldn't, I mean, in terms of the endoscopic I would ignore things like petechia and stuff and just focus on the ulcers like we talked about. I think all three of those complications -- perforation, bleeding, and obstruction -- are serious enough and basically always require -- virtually always require hospitalization that I think most of us would agree, assuming we defined it right, that they would all be serious and you don't need to prioritize.

I mean, everybody knows I think in general, perforations are probably the worst thing to have, so perforation is worse. It's also a lower incidence than is bleeding. But bleeding is quite variable in terms of -- and specific -- in terms of severity as well.

CHAIRMAN PETRI: I suppose that your consensus panel could weight the different things? There are lots of possibilities. The third question we've been asked to address is, what constitutes an adequate length of study or studies to support changes to the NSAID GI Warning?

And we talked a little bit about endoscopy. I think we were offered a few choices. One was zero, one, two, three months; the other was zero, one-and-a-half, three, and six months. But does anybody have a preference? Do we think those are equal? Dr. Laine, do you want to --

DR. LAINE: This is so difficult. I mean, you can probably argue lots of different ways. I personally am not a believer in doing too many endoscopies because then you start finding -- you know, if you do an endoscopy every day you're going to find more ulcers. So you probably don't want to do too many endoscopies.

The question is, is it one, two and three months; do you do six weeks and three months; do you do six weeks, six months? The question really -- I think the harder question, is three months fine?

Most of the studies have done three months and it does start to -- it seems that the curves start to flatten in three months. Or do you want to require six months seeing if there's some difference with COX-2 or -- you know, just to pick up those few extra.

I mean, in general it seems that if you're going to require the clinical studies, you can perhaps get away with a shorter term endoscopic study. So I

would probably -- I might err on the side of shorter on the endoscopic if you're going to require the clinical study anyway.

CHAIRMAN PETRI: Okay. Any other opinions from the committee? Audience questions?

DR. AKURA: Mirang Akura from Yukon. Having done many of these studies in the literature as you've seen, most of the studies are usually three months -- some variation of them, that is -- one month, two months, and three months, or six weeks or three months, or a variation from baseline to three months.

And I think those give us reasonable answer as far as predictive value or importance as far as it's concerned -- as far as NSAIDs or these other drugs are concerned. Six months is really not necessary and doesn't add any new information that we don't get at three months.

CHAIRMAN PETRI: There seems to be a reasonable consensus that endoscopy trials can be three months. And then as Ken Johnson had discussed, the length of time for the clinical outcome will depend on the number of patients and the event rate.

Any other committee comments? Dr. Hyde.

DR. HYDE: The length of study -- I mean,

there wasn't so much to put the statistical question to the committee, but you know, what sort of minimum duration would they really feel comfortable? They understand the profile and the time course.

You know, ideally you'd like to go for years but of course that's unreasonable. Is six months enough or are you concerned that something might evolve over the period of a year that you know, you would be more comfortable with that?

CHAIRMAN PETRI: Let me ask Dr. Laine to address that.

DR. LAINE: Well, obviously nobody knows for sure with the new agents, but if you look at what literature is available, I mean, the question -- most people suggest that there is either an increased number, a higher rate in the first few months -- or in other experimental studies there is a linear increase over years.

So one would think at least, that by six months we don't have evidence that from six months to 12 months that we're going to be changing the rate -- i.e., accelerating. Although Dr. Singh did make a comment that I was understanding that perhaps that might happen.

But everything else that I've seen at

least in press, either suggests it's like this or like this. If that's true then six months probably is adequate -- at least from the -- on the old NSAIDs I would think.

Certainly, in terms of the number of events though, there may not -- you know, you're looking at perhaps three-quarters of one percent at one year in the mucosa trial which is actually -- at six months actually -- in the mucosa trial which is actually high end of other studies.

They had a higher risk group. Half their patients -- 42 percent, to be exact -- were on steroids. You know, they were older, all RA patients. So it might even be lower in studies that would be done today.

CHAIRMAN PETRI: I think Dr. Singh wanted to address the point of the slope.

DR. SINGH: Right. What we found was the slope was a constant line. There was a little -- as Loren mentioned -- there was a little, maybe a little blip; hardly detectable and certainly not statistically significant. But the hazard rate was a straight line between zero to 13 years.

What I meant that the slope needed to go up was that at 13 years the slope needed to go up, and

at 13 years, by this time you're also 13 years older. But if you took out the age effect out, then it was a straight line; and it's virtually as good a straight line as you see in the biological system.

But remember, that's with the currently known NSAIDs. But if you believe that this is a new class of compounds and they may be doing something that we don't know about, then is it reasonable to presuppose from the currently known NSAIDs that that's what these components would also do?

Is it theoretically possible -- at least theoretically possible, that maybe these components will start to lose whatever effect they may have or may not have, and might cause more ulcerations from six to 12 months? I don't know. I mean, this is for the committee to decide.

CHAIRMAN PETRI: I think we're just trying to construct a reasonable framework given current knowledge.

DR. SINGH: Yes, but you might require them in the post-marketing surveillance kind of an environment that they will be studying these for longer periods of time and then you would know what happens after registration.

CHAIRMAN PETRI: Dr. Simon.

DR. T. SIMON: Dr. Singh, actually I think, put his finger on the issue. There is a difference in the rate of occurrence of PUBS and the rate of detection of endoscopic ulceration -- particularly prominent during the first three months.

If this is a new class of agent -- we believe it is -- one gets additional information by going beyond that first three months to make certain that you're beyond whatever short term phenomenon -- whether it's adaptation or something else -- goes on during the three months to really want to be sure you're looking at those ulcers that are happening during the three to six month period and if you think they might be different.

You get a good look at that by going the additional period and making the additional observation.

CHAIRMAN PETRI: Do you think you would lose that much by having just a 3-month study?

DR. T. SIMON: It depends on how well we think we understand what goes on during that first three month period of time. I mean, people talk about adaption; the biology of that is unclear. You're clearly beyond it if you go to six.

CHAIRMAN PETRI: Dr. Silverstein.

DR. SILVERSTEIN: Just wanted to comment. Just, one of the studies that Loren pointed out was a study by John Carada which looked at the risk rate for duodenal and gastric events over a 36-month period, and remained remarkably stable, also supporting what Dr. Singh said; that there's a very straight line.

And therefore, I support the concept at six months. And also in the mucosa trial that kind of seemed to work -- that six months seems to give you a good indication of what's going to happen. I'm not aware of any data that suggests that there's a delayed kind of a hockey stick, but rather that it's in a straight line, and I think Carada's evidence adds to the Stanford information.

CHAIRMAN PETRI: If you could stay at the microphone just for one second. Six months is nice; is three months wrong?

DR. SILVERSTEIN: For?

CHAIRMAN PETRI: Endoscopy.

DR. SILVERSTEIN: No, I think for endoscopy three months is adequate because in the four or five studies I'm aware of that have looked beyond three months, the curve -- there is this initial -- initially there may be a slightly higher risk in the first month or two, and then after that the curves

remain -- might be in different areas because of what they got to in the first two or three months.

But then they remain essentially the same relative to each other. So once again, I would think three months is adequate for an endoscopic study and I probably would go six months for a --

CHAIRMAN PETRI: A clinical?

DR. SILVERSTEIN: -- clinical outcome study.

CHAIRMAN PETRI: Thank you. Dr. Johnson?

DR. JOHNSON: Yes, I just wanted to underline the uncertainty that Dr. Singh mentioned. I mean, in a sense what we're doing is flipping the scales here. The drug is going to be approved for efficacy, presumably, and if this is a Phase IV, randomized study then the next claim that's going to come in is going to be a safety claim.

And you know, normally we just let safety sort of fall out of efficacy trials and describe it in the label. But in this case it's going to be the other way around. Whether it's pre-approval or post-approval it doesn't matter; the sort of intellectual dynamic is the same.

You're designing your study to address safety directly, and the efficacy may or may not fall

out. We haven't talked about that -- or maybe it should or shouldn't fall out. By purely in terms of safety we don't know whether three months, six months, twelve months, two years, or five years. I mean, it's black box right now.

And to the degree that we're willing to extrapolate from the non-steroidal world is our only reassurance at this point in time. But the flip side of that has occurred in the past, too. When we approve things for efficacy we tend to set some sort of arbitrary -- and it is arbitrary, I think, in the end -- some sort of duration of trial.

And the issue always is, does the drug wear off? I mean, I think like Ken mentioned this morning, probably all non-steroidals wear off in osteoarthritis and they probably don't do anything long-term. I don't know. But we still have to make some kind of arbitrary time duration call, and that's why we're very interested in your feedback about, you know, a safety design trial which I think is the first in rheumatology.

CHAIRMAN PETRI: Dr. Witter, our comments have addressed your questions? The next question is number 4: In these studies, what dose and type of study comparators should be used; i.e., placebo, other

NSAIDs, the "X" dose of the test product, etc.?

We discussed this a little bit, but if we can just make sure we've actually reached a consensus. I'm afraid to ask Dr. Yocum, but maybe we'll start with you.

DR. YOCUM: Remember again, I believe in placebos in the safety trials. The question here is whether it should be 3-arm or 2-arm -- placebo with an active comparator. And I guess the comments earlier by Dr. Weintraub concerned the power of a comparator to placebo. And if in fact, these drugs are like placebo, what does it take power-wise? I guess we need just a full evaluation of that.

CHAIRMAN PETRI: Well, in an equivalence trial it's really what you consider to be clinically important. It's the clinically important difference. Could I ask some of our biostatisticians to comment a little bit about powering equivalence trials?

AUDIENCE PARTICIPANT: Powering is done -- in a clinical equivalence trial one has to define what do we mean by the clinically equivalence first? You know, we call it (unintelligible).

And then we have to have the middle of clinical efficacy, is it treatment -- is it different from placebo on a direct scale, different scale? Are

we looking for the -- ratio? We have to define some kind of measure.

And we have to construct the lower confident bound for that -- 95 percent. If that lower 95 percent confidence bound falls within that clinical (unintelligible) we say it's (unintelligible), otherwise not.

And to power such a trial, the power depends on what is the delta, you know? Because the smaller the delta, the larger the size. And also you know, the power depends -- if you are looking at the rate, you know, if the response rate is low the power will be different; if the response rate is high the power will be different.

And one could put the whole theory, the statistical theory in the frame of one-sided tests. For example, you may like to say that the hypothesis is that they are not equivalent. That means the increase in the arc ratio is 20 percent or more. That means you don't want that; it's not equal.

But then the alternate hypothesis which you want to accept or reject is now that the increase in arc ratio is now is less than 20 percent. So one could put in the framework of the testing hypothesis and we can define the outcome and so forth, and what

(unintelligible), no problem there.

But usually when the incidence rates are small and we are looking at increases of say, 20 percent or less, the sample size remains pretty big. So IC's trials and those trials have been done on similar lines and you know, there's something (unintelligible).

CHAIRMAN PETRI: I actually see this as another set of hurdles safer than another NSAID, and then a higher hurdle is, as safe as placebo. And I would assume the labeling would have to reflect that set of hurdles.

DR. YOCUM: I guess I would ask, since Ken has done a Tylenol™ study in OA, would you feel comfortable --

DR. BRANDT: An acetaminophen study.

DR. YOCUM: Yes, sorry, acetaminophen. I apologize -- acetaminophen trial. I mean, if you got good power would that be acceptable to you, versus placebo at OA?

DR. BRANDT: Yes, of course in that study we did not have a placebo group and we used two different doses of an NSAID against acetaminophen and showed roughly equivalence.

CHAIRMAN PETRI: Any other thoughts? Let

me ask Dr. Witter, do you have other specific questions here? Dr. Hyde, anything else under that question?

DR. HYDE: With number 4, I guess the one element of that was the "X" dose of the product and how we might decide that and how, you know, should we test above that and how far above that?

CHAIRMAN PETRI: I guess you could go the other way by that ad hoc committee that said just don't use them at all. Any thoughts about "X" dose comparison? I think as clinicians we only want to test the clinically effective dose, in terms of safety. Dr. Simon?

DR. SIMON: I guess Dr. Hyde, the reason you're asking that question is that if this is an argument about selectivity, if you're then changing your selectivity when you go to a higher dose, that perhaps your tolerability and toxicity profile would change in the shift of selectivity?

Or are you asking a more general question that you would always want to know two times the normal, effective dose from a toxicity point of view? Is there something unique to the biology of this drug that you're asking about that?

DR. HYDE: Well, I guess, in particular

since there's the prospect of an enhanced safety claim, the temptation is always going to be well, I'll just titrate to the same old safety and maybe get more efficacy.

DR. SIMON: Okay, so then the question would be that in the normal, everyday activity of most clinicians they sometimes try to push the envelope and go higher to get more efficacy, and we'd like to know the safety issues in that. And if that's in fact, shown by your experience, then in fact, I would be uncomfortable without knowing what would happen at a higher dose, if in fact your expectation would be it will be used at a higher dose.

You would have to tell me whether or not that would be two times or whatever has been the typical experience, but I think we should do what is typically happening in the real world under those circumstances.

DR. WITTER: I think Ibuprofen™ was registered I think, at 900 milligrams and I think the top dose now is 3200 --

DR. SIMON: It's 36.

DR. HYDE: -- as an example.

CHAIRMAN PETRI: Dr. Fernandez-Madrid.

DR. FERNANDEZ-MADRID: From experience,

realized that some authorities have used a higher dose than the dose recommended for many compounds. So this is going to happen, so we would like to know what happens with a 2X dose.

CHAIRMAN PETRI: I'm sorry, Dr. Weintraub.

DR. WEINTRAUB: I'm sorry. Well, we are interested in the other part of Dr. Simon's question. That is a very real point which has existed in all kinds of drugs in every kind of situation; whether it's in our hypertensive agents, whether it's beta blockers, whether it's gastrointestinal agents.

Every type of drug pushed to its maximum will lose its selectivity -- we think. And so we want to know if, not only should we do 2X but maybe something even higher.

CHAIRMAN PETRI: Dr. Abramson.

DR. ABRAMSON: I have some concerns about that. I mean, that's why we had Phase I in early studies, I think the dose one. I think the history of the NSAIDs being raised is that we didn't recognize back in those years that the analgesic effects might have been giving us some therapeutic benefit and we had to go higher.

But I think the experience of taking a drug that comes to good clinical studies at "X" level,

to double it, you're going to be asking for toxicities that would be -- it might put patients at risk for these long-term --

CHAIRMAN PETRI: But Steve, let's balance that with, what if at a higher dose it's a -- this is a special class where this may be important.

DR. ABRAMSON: Right, well I think that -- I agree with you, Michelle; that's another question. If you -- it depends what your asking. For safety issues I think it would be unfair and possibly dangerous to double the dose just to find out if other things happen. I think that's setting the bar real high.

But if you take the other issue though, is that studies ought to be set up that if you can, push these drugs to higher levels because they're safer. That's the hypothesis that maybe you can get more prostaglandin inhibition -- that we've been getting away with 40 percent prostaglandin inhibition and maybe you could push these drugs higher -- that's a study that I think could then be designed and toxicity looked for.

But I wouldn't, just for the sake of getting GI labeling, make you double the dose. That's like giving 400 milligrams of Motrin™; we know 40

milligrams of Feldene™ ripped up stomachs. When you start doubling doses you get into trouble.

I think if you want to design other studies to look at, you know, other effects of COX-2 inhibitors at higher levels, that's a separate clinical study.

CHAIRMAN PETRI: But if those studies are going to be done post-marketing, don't we need to have some idea about toxicity of the 2X dose pre-marketing?

DR. ABRAMSON: Not for the label --

DR. SIMON: But you'll note that, because some of the Phase II and the dose ranging methodology will determine what the effects are at a 2X dose. Now, Michelle the --

DR. WEINTRAUB: I'm sorry, just let me say one thing. We know that the dose response curve is relatively flat with these things, and the question is, is it going to be relatively flat for the selectivity and is it going to be relatively flat for the toxicity? Because we know that these drugs will be used over the labeled dose.

CHAIRMAN PETRI: Dr. Johnson, did you have a comment?

DR. JOHNSON: Well, it's essentially what Mike just said. You know, traditionally in rheumatoid

or in OA, maximal doses have been selected by pushing the dose to toxicity and then backing off a little bit. And it may not happen as prominently in these development plans.

So we do have an issue where we don't have experience from the past, and Ibuprofen™ is not really a good case-in-point because, you know, presumably at 3600 or 4000 you get GI toxicity or whatever. But you know, these drugs may be different, and it may be interesting to discuss whether there should be a component in their development that addresses this.

DR. LAINE: But I'm hearing that efficacy -- I'm sorry -- if efficacy is not improved by doubling or tripling the dose, then I don't quite understand why we would want to triple or quadruple the dose for safety measures. If it was then it would make sense, perhaps, but if there's no -- I mean, if that's what I'm hearing, then why not just study the maximum effective dose?

CHAIRMAN PETRI: Dr. Brandt.

DR. BRANDT: That's true also for some of the NSAIDs that are currently on the market, like Ibuprofen™. That does not eliminate the -- that doesn't preclude patients if not doctors, pushing that

dose to try to obtain better analgesic.

CHAIRMAN PETRI: Dr. Moreland.

DR. MORELAND: I just want to concur I think, with Steve's comments. I think the time to find out that dose that's most effective is in a Phase I study, not to be messing around in a Phase III study. We may use it in higher doses, but then let's let the company go back in a well-designed Phase I study and tease out that. I just think this is --.

CHAIRMAN PETRI: Dr. Singh.

DR. SINGH: Let me give you an example of what happened in real life, and actually, this goes beyond Ibuprofen™. We looked at, I think, 11 different NSAIDs and we published this over three years ago in American General Medicine. We called the article, "From Experiment to Experience".

So what happened was, when we looked at what were the doses that these NSAIDs in all the clinical trials were tested at -- at least the published clinical trials that we were aware of -- and what doses are they getting used at, except for Ploxican which seemed to be used at pretty much the same 20 milligram dose, almost all the other NSAIDs, the dose in the clinical trials was only about 60 to 70 percent of what the median dose that people in the

actual observation groups were using.

And of course the second example that didn't work along this was aspirin, because I think the FDA required all drug companies to use at least four grams of aspirin as a comparator. So all the clinical trials have four grams of aspirin but the actual dose within the community setting was much less than four grams because people don't take four grams of aspirin.

So Dr. Brandt is absolutely correct; that the dose creep does occur, and it a very real phenomenon and it occurs in things with -- a group with all the NSAIDs -- Naprosyn, Tolectin -- I mean, every single NSAID except Feldene™ and aspirin.

CHAIRMAN PETRI: Does the committee feel comfortable with looking at the 2X dose in terms of toxicity? Anyone object to that?

MS. MALONE: I just -- I have a --

CHAIRMAN PETRI: Ms. Malone.

MS. MALONE: -- a problem just, when you talk about the dose and efficacy, okay, the reason that the rheumatologists are suggesting that you increase the dose is because the dose that it was tested at, is it working for this patient? Okay, so that -- I'm really confused here.

CHAIRMAN PETRI: Well, we're asking about toxicity data now, so for an average patient dose "X" appears to be optimal for efficacy, but for toxicity data do you want to know what the 2X dose does? Because there will be this off-label use. I like the word "dose creep". I hadn't heard that one before.

Dr. Abramson, you had a comment?

DR. ABRAMSON: Yes. I think we need to hear other people's opinions. I'm not sure -- see, my sense is that, as maybe Larry says, those dose finding issues get done early-on. And I don't know what the precedent is.

If you have a blood pressure medicine, say I'm going to double the dose for a group of patients and see what happens. We may end up with toxicity we don't anticipate; we may end up with renal toxicity. I have grave concerns about using this as a -- treating these drugs differently in this regard.

I think we're confusing a couple of things. You know, there's the issue of whether it's COX-2 selective at the higher concentrations, and I think there may be ways, when you get up to 80 percent inhibition of COX-2 is your drug also still COX-1 selective? And there may be surrogates looking at platelets and other things to see if it's still COX-1

selective.

But I have grave concerns about putting this as part of the GI toxicity bar and linking that to the endoscopy studies and the clinical outcome studies. I think we should go with the efficacious dose.

CHAIRMAN PETRI: Wouldn't that be tremendously useful to the clinician to know you shouldn't dose creep?

DR. ABRAMSON: That's --

DR. WITTER: The "X" dose, it really kind of gets out the issues of -- registration is one facet, obviously of the drug development, and GI safety as Ken has pointed out, is certainly a component of that as are other safety issues. But to induce labeling changes, I think is really where the "X" dose comes into play.

CHAIRMAN PETRI: You brought this up, the "X" dose, so can you tell us, is there any precedent for testing the 2X dose?

DR. WITTER: I don't know if I'd want to take credit for bringing the "X" dose up. It's a concept, I think in terms of, if somebody wants to have a label change, the thinking is that -- for example, looking at the COX-2 agents they should be so

safe -- they are so different, that it doesn't matter if you give it as much as you can.

You're not going to have any in this instance, increased GI toxicity. So therefore, the dosing really is kind of irrelevant in that regard. But it's mainly to be looked at in terms of how the label can be changed.

What you can do is take for example, your favorite NSAID and half the dose, and then go back up to the usual dose and start looking at GI endpoints that way, then one could envision changing -- that all the NSAIDs would have all their labels changed.

And I don't think that's what you would want to see as a clinician if the GI Warning section is altered or removed. What you I think, want is something that is substantially different from that, that you can say, this isn't like if I give "X" NSAID or if I give twice-X NSAID, because you wouldn't do that. You'd be so concerned about toxicity.

So I think there's a distinction needs to be made between registration and any induced label changes.

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: I rest my case here as relating why we should not be looking at this as a

non-steroidal, and that's exactly the reason. We have a real problem here.

We spent a large portion of the day talking about something that may not be applicable to these drugs, and I'm very concerned about actually high grade, long-term inhibition of COX-2 activity as opposed to some very obscure potential side effects that may be actually, quite unique to this drug. And I'm not entirely sure that we know how to evaluate those and we've not discussed them yet.

DR. WITTER: Right, that's question 3.

DR. SIMON: No, I understand that. And I'm concerned that the issue of the twofold or onefold, or whatever it is that we're presently discussing now, as a relationship to it being COX-selective, I think we need to recognize that if this is a new drug, we have to define what it means to be a new drug and what those criteria are going to be.

Are they going to be the therapeutic effectiveness at the same time it does not do *X*, *Y*, and *Z*, as you would predict based on the biology? If indeed, we achieve that definition, then -- like in any new drug that comes along, we're interested in knowing the toxic effects of these drugs.

And we should be designing the trials to

ask those questions, not to be prepared to expect that they do something that they never do.

DR. WITTER: Dr. Simon, I think the sponsors have been doing the studies moreso on their own then -- I mean, if they thought this was an antibiotic that had anti-inflammatory effects, I think that's what they would have come forward with. But the sponsors for the most part, are doing these kinds of studies.

DR. SIMON: But they may be doing it because of the discussion that's going on here, which has to do with the fear of it being labeled as a non-steroidal and not having the data that proves its safety. I'm not sure who's driving what here. I'm not entirely sure the industry is driving this as opposed to the confusion about how to evaluate its outcomes.

And I see why you're concerned, but you know, if you do it -- I guarantee you, if you use either product that presently is in whatever trial stage it's in five times the therapeutic dose, you'll probably get COX-1 effects.

Now, will anybody actually ever do that? And I'm not sure that that's an appropriate question to ask, unless you go back to a Phase I trial. And I

certainly wouldn't want to burden a Phase III trial with this kind of question. I'm much more interested in some other stuff than this.

CHAIRMAN PETRI: Dr. Yocum first, and then Dr. Katona.

DR. YOCUM: I'm only a little concerned. This X dosing or 2X dosing, is this to be for the outcome to the GI or is this to be the endoscopy, or would one follow the other; i.e., if you found your 2X dose had serious ulcerations and problems, would you then proceed with an outcome or would -- I guess I'm a little confused there as where this "X" dosing comes in.

CHAIRMAN PETRI: I would assume that that is logical. If you found increased endoscopic problems you would have to then follow with the clinical outcomes as well. Is there other thoughts about that? Dr. Katona.

DR. KATONA: I'm just wondering about the clinical relevance of this 2X dosing. It seems a little too high to me. I think if I think back of a clinical example I think we might go up temporarily to 1500 milligram of Naprosyn™, but we keep most of our patients under 1000 milligrams.

I'm not sure that I would go 2X. It's

very rare that we ever do that. So I think it's a very good idea but 2X might be a little bit too high.

CHAIRMAN PETRI: So I think what's happening is, no one is quite sure what is the upper bound dose for toxicity studies. There isn't a real consensus. So why don't we move on to the next question which is really a sub-population question.

"What type of patients and medications should be included or excluded for these studies; i.e., OA vs. RA, H. Pylori, concomitant medications, etc.?"

Other thoughts about large disease groups that should be studied? Dr. Pucino.

DR. PUCINO: For the endoscopy studies, probably it should be high risk groups versus very select, exclusive groups. For the outcome studies it should probably be all-inclusive to account for the confounders by out of subset randomizations, just to assure that you do have equal groups -- homogenous groups?

CHAIRMAN PETRI: Dr. Laine, thoughts about this?

DR. LAINE: Well, I might actually be a little bit opposite, and that is, I mean, the high risk groups in the outcome study where they're not

getting endoscopy -- where it's kind of a real world situation -- the endoscopy study is where, if you're going to exclude the highest risk patients it seems to me that's where you would exclude them because you don't need them as much -- if you know what I'm saying -- just to see the ulcer.

All you really care there about is seeing an endoscopic ulcer. It's really the clinical outcome study where you want to have that real world, high risk patients even more. So if I had to choose one or the other I would put them in the clinical outcome which didn't require the endoscopies; we're just following the patients.

CHAIRMAN PETRI: Other thoughts? Dr. Fernandez-Madrid.

DR. FERNANDEZ-MADRID: I think in the rheumatoids I would definitely include a subset with methotrexate and particularly with Prednisone™.

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: Yes, and I would urge that these studies, if patients are going to be recruited who are on glucocorticoids, that the studies reflect exactly how the glucocorticoids are used and we should strategy somewhat on dose in a broad manner.

I think there was some allusion in

previous documents to questions regarding stratification, and I think that it should be stratified based on risk factors, based on the presence of Helicovacular Pylori or not -- not to exclude them but to stratify based on its presence, so we can understand more about that.

And I, in contradistinction to Loren, would be a little more likely to do an endoscopy trial for high risk patients than a longer-term outcomes trial without giving them prophylaxis, if that's what was decided to do.

I'd be uncomfortable for a 6-month outcome trial for a high risk patient not on prophylaxis.

DR. LAINE: Yes, but these studies presumably, are only people who are -- physicians are using NSAIDs on already. So this real world, clinical outcome study is not going to be -- is going to be using people who are already on NSAIDs.

DR. SIMON: And are on prophylaxis as a result.

DR. LAINE: Well, that would probably -- I would assume excludes somebody. If the physician feels that they require a proton pump and commuter Misoprostol or high dose H2 reciperantagonist, I would think they probably wouldn't be on that study to begin

with -- if the physician felt they had to be on that for good.

DR. SIMON: But then that wouldn't give me any good data about what I know to understand is the problem with high risk patients. So that's my being uncomfortable.

I prefer that to be in the endoscopy trial, shorter-term, drop out when you get the ulcer, much more control over what happens to that person; as opposed to just watching to see what happens and maybe giving them endoscopy or not.

That's my own personal bias.

DR. LAINE: Okay.

CHAIRMAN PETRI: Let's talk a little bit about H. Pylori. The thought was it would be noted but not treated. Is that correct, Dr. Laine?

DR. LAINE: Correct, because I think right now we don't have -- almost no organization would suggest treating non-ulcer patients who have H. Pylori. And I think that it really wouldn't be reasonable to test and treat -- I mean, treat everybody just because if they have H. Pylori.

If they had an ulcer when they had H. Pylori, yes, then you would treat them I think. I think that's obligatory.

CHAIRMAN PETRI: Dr. Silverstein.

DR. SILVERSTEIN: I just want to respond to something Lee said. Lee, I would definitely stratify by risk in a smaller trial, because there the disaster is to find out that 47 percent of the people in group A were on steroids and ten percent of group B.

But my point was at a very large trial with 4,000 or 5,000 people, it naturally does that. And I think, as you know --

DR. SIMON: Yes, I would agree.

CHAIRMAN PETRI: Dr. Singh.

DR. SINGH: Two points. Lee, about Prednisone™. Of course, Prednisone™ is an important risk factor but more important in the tools that we found is the length of time a person is on Prednisone™. I think that should be taken into consideration, too; that not only does Prednisone™ matter but it's the length of time that's more important than dose.

And secondly, I mean, I'm sure people around the room recognize, but the incidence rate of serious ulcer complications is different in rheumatoid arthritis as compared to osteoarthritis. So that needs to be recognized that not to lump those two

things together. And RA rates are really one-and-a-half to two times higher than the OA rates are.

CHAIRMAN PETRI: Although we haven't mentioned, I think we all agree that the elderly and our population of children with JRA should be included. Dr. Liang, you have a comment?

DR. LIANG: Well, I just wanted to - this is not news. We're too focused on the lumen. Once the genie's out of the bottle everyone who's on NSAID now who's ever had a problem or were going to have problem, is going to get this.

So I'm concerned that some of our autoimmune disease might actually be adversely affected by these agents -- such as lupus and whatnot. And so I'm one, again, looking for effectiveness trials in real world so I can get some information that will help me in my office.

And I could see actually, lumping some of these, you know, patients with unusual risk factors for either GI or for cognitive, or for bone, and to sort of use those as co-variants in the analysis and use large numbers to sort of balance off the group. And be very permissive; just collect the data and analyze it.

But I'd like to see as many patients that

would get it in the real world, in these trials. Because this is the last and only time that we're going to do these studies, you know, I think with careful attention to ascertaining all the side effects.

CHAIRMAN PETRI: To elaborate on what Dr. Liang said about Lupus patients, there's a special concern about Lupus patients and NSAID, meningitis, hepatitis, and decrease in creatinine clearance. So that's an issue that we haven't really discussed.

A question from the audience.

AUDIENCE PARTICIPANT: Understanding the rationale for testing for H. Pylori so that that will then be understood better -- what test should be used?

DR. LAINE: Well, I think clearly in the outcome study where endoscopy is not required necessarily at baseline, it would be a blood test, an antibody test. But in the endoscopic study, since you're doing endoscopy anyway, I personally would use an endoscopic biopsy test since the cost of the endoscopy has already been undertaken.

CHAIRMAN PETRI: Dr. Moreland.

DR. MORELAND: I guess to ask the question about concomitant use of aspirin and whether that's going to be allowed or not, I'll start the discussion

or argument, that we should allow that to be used.

DR. LAINE: All doses or just vascular prophylaxis doses?

DR. MORELAND: Vascular prophylaxis doses.

CHAIRMAN PETRI: I think it's going to be an important issue because we're gong to see that more and more widely. Other thoughts about low-dose aspirin use being a special sub-population? I'm seeing a lot of nods of yes, that that's going to be important.

Any other thoughts about special sub-populations? Yes, Dr. Harris?

DR. HARRIS: In the special sub-population over 65, with prophylaxis or without prophylaxis? And in terms of designing, you know, if you're going to compare a population of patients.

CHAIRMAN PETRI: Well, I think what we said before was without prophylaxis, because that's the clinical question. Dr. Simon.

DR. SIMON: I actually favor, in the endoscopic trials with prophylaxis for any high risk characteristics based on the impression of what high risk means. That's one of the risk factors so therefore it's a high risk patient. I don't think we should do that in the outcomes trial.

DR. LAINE: I think if you do that you really should have a separate trial. I mean, then the question you're asking is, is this new agent as good as a standard NSAID plus Misoprostol, for example. And that's a question that somebody might want to ask -- I'm not sure they would -- but if they want to ask that, that's fine.

But that's a -- I'm just saying that's a different question. So if you want to pose that question in the high risk group it's fine, but I think it messes the study up or kind of confounds it if you're starting to throw that group in with the other things.

DR. SIMON: But I'm not doing it to mess or not mess up the study; I'm doing it to find out the answer as to whether or not these are equivalent to, better than, non-steroidals that are presently available. And to me, the state-of-the-art is, high risk patient, non-steroidals presently available, they have to be prophylaxed.

DR. LAINE: And all I'm saying is, I would do a separate -- I think that's fine, but then you just do a separate study of that -- is how I would handle it, anyway.

DR. SIMON: Okay.

CHAIRMAN PETRI: Because they are different questions. Now, I'd like us to quickly discuss number 6 and then take a short break. Number 6 is on: What statistical analysis should be used for these studies to support changes in the NSAID GI Warning?

I think we talked a little bit that one hurdle would be superiority in GI safety over another NSAID. The next hurdle would be same as placebo. Let me ask Dr. Weintraub: was there a different issue that you wanted to get at?

DR. HYDE: Well, I guess -- yes, to put the spin on, particularly of interest would be what you perceived as equivalent to placebo, and how different a rate you might still accept as placebo-like. And particularly in the cases where the underlying placebo rates are very low.

CHAIRMAN PETRI: I think that's best addressed by a consensus conference.

DR. LIANG: No, that's addressed by the placebo group.

CHAIRMAN PETRI: But for an equivalence trial though, clinicians have to determine what the important difference.

DR. LIANG: But if you're just asking

whether there are more GI bleeding in one group or the another -- if you're asking about the GI issue, you're just asking what the differences are between the placebo and the active group.

DR. HYDE: Right, but I guess it has to do with --

DR. LIANG: You don't do this by committee; you do it with data.

DR. HYDE: -- elimination of the GI Warning or substantial modification of the GI warning. You know, what would you like to see; what would you view as being not just on the spectrum, but actually something different.

DR. LAINE: Wouldn't we just have to determine what 95 percent confidence or the difference we would accept as the same, basically? As comparable? That's what you're asking, basically.

DR. HYDE: Yes, I'd like to see some discussion.

CHAIRMAN PETRI: Let me as Dr. Laine, what would you take as the placebo rate of GI bleed, perf, and obstruction?

DR. LAINE: Well, as you heard, I mean, it would be somewhere -- if we took, the mucosa trial the number I used from there is three-quarters of one

percent at six months. I think that's a higher risk group and I'm not positive that we would have that high a group in a new study so I would probably have to go -- I might go lower just to be safe if I were doing the study. And whether a half-a-percent a year -- that let's say, is a reasonable number, perhaps.

CHAIRMAN PETRI: So if we're given a placebo rate, might be half-of-a-percent. Any committee members want to just estimate for us what --

DR. LAINE: Dr. Silverstein may --

CHAIRMAN PETRI: -- they feel would be a comfortable difference to say something was the same as placebo? This again, is just your clinical judgment --

DR. LAINE: Let's just say one percent a year to make it easy, if you want.

CHAIRMAN PETRI: So if the placebo rate is somewhere between point-five and one percent, how much higher would you allow drug *X* to be, to be equivalent to placebo? Would you allow it to be 1.5? This is going to power the study as well, of course.

AUDIENCE PARTICIPANT: May I just make a comment? That placebo that you're talking about is a rate of NSAID plus placebo. That's not the true placebo rate. I think what you mean by a true placebo

rate is the patient with rheumatoid arthritis, not given an NSAID. What is the rate of -- you see a complication there? Because if you're going to put your placebo versus a COX-2 component, isn't that what you're going to be doing?

DR. LAINE: I understood you to mean the NSAID rate, isn't that correct?

CHAIRMAN PETRI: Well --

AUDIENCE PARTICIPANT: There's a difference.

CHAIRMAN PETRI: Yes, there is a difference, so what we're talking about now is the NSAIDs saying they are the same as placebo.

DR. LAINE: So what we want to -- they're new NSAID?

CHAIRMAN PETRI: Yes, new NSAID; COX-2 NSAID. Is it the same as placebo?

AUDIENCE PARTICIPANT: So then you want to know the true placebo rate? What is the rate of a serious GI complication in the group of rheumatoid arthritis patients, not treated with an NSAID? And that rate is close to point-two percent; in fact, it's about point-one-nine percent as we estimated with 6,000 patients --

CHAIRMAN PETRI: If it's point-two percent

we have to say as clinicians, what would be equivalent to that? What's the highest bound that you would say was equivalent? And I'm not sure anyone has ever thought about that or -- not a dinner table conversation.

Like, you know, would people feel comfortable that it should not be higher than point-five percent if the placebo is point-two?

DR. SINGH: Let me sort of try to put that in perspective. Let's also tell you what are the rates are of some of the other NSAIDs. Ibuprofen™ is about point-6 percent -- about point-7 percent; salicylate, which is what we are talking about is one of the safer NSAIDs, is about point-5 percent or about point-55 percent. Now, would you want this NSAID to beat the salicylate rate?

CHAIRMAN PETRI: Yes.

DR. SINGH: So then you want to go lower.

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: In this case, I think in asking the question, if you're equal to placebo as opposed to other things we've talked about before, I think whatever the statistical parameters that suggest it's within the 95 percent confidence intervals of being the placebo rate, would tell me that it's

placebo.

I would actually be very inflexible about that. If there is any rate that is different, that's increased over the placebo, beyond the 95 percent confidence intervals, would tell me it's not doing what I thought it was supposed to do, and thus it is a non-steroidal, anti-inflammatory drug and deserves the rest of the conversation.

DR. LAINE: So what you're saying Lee, is that if the upper bound of the 95 confidence interval of the placebo is point-eight --

DR. SIMON: Whatever it is.

DR. LAINE: -- it has to be less than point-eight is what you're saying?

DR. SIMON: Exactly.

CHAIRMAN PETRI: I think we need a biostatistician here to help us. In an equivalence trial it's not determined by statistics. The clinician has to say what they except.

DR. SIMON: Well, that's what I accept, as the clinician.

CHAIRMAN PETRI: Dr. Silverstein, first.

DR. SILVERSTEIN: Yes, well actually, a bunch of us have thought about this, and we have sort of concluded exactly what you said; that it is the

clinical question. So it's two comments.

One is, the aspirin issue is an interesting issue and in the placebo group, you know, if you took a survey of the group here and said, you know, 55-year-old gastroenterologist, what would be my rate? Most people would think it was going to be really low on having a complication.

But the problem is, 40 or 50 percent of people are on salicylates. So that is going to increase the placebo rate beyond what you think it might be.

The second things is, because it's so difficult, Lee, to do what you said -- which is to prove that something is statistically not different than some thing else and requires huge numbers -- one other approach -- for example, and ulcer rate -- one other approach would be to go to the complication rate and then use clinical judgment. And this is what I mean.

So let's say you've got 1,000 people, and let's say the rate on a standard NSAID is two percent. So that's 20 people having a complication out of 1,000. And let's say placebo is half-a-percent. So that's five people. So placebo of five, a standard NSAID is 20 out of 1,000, and then use clinical

judgment about, what would a clinician say?

I can't tell the difference between five and seven. Or you know, five and eight. Not use statistics, but rather use sort of a clinical judgment. And do what you did which is to say if it's below ten, maybe you know, below eight. But come up with a proposal that way rather than trying to prove statistically that it's equivalent to placebo, because I'm not sure it can be done.

CHAIRMAN PETRI: Actually, Dr. Singh.

DR. SINGH: We have given it considerable thought as well, and in fact we have been working with our statistician as to how we design to look at these rates -- but I'm not going to go into the details, but that is what we do all the time. And what of the things that what you're suggesting, Lee, we discussed that very carefully and yes, you could do that.

The way you would do that is to assume -- and I think I'm going to take some of the things that Dr. Hawk is going to say -- that you assume that the background rate is point-two percent, and then there's not a 95 percent confidence interval that background rate. That's not the say to do statistics.

You assume that's the fixed proportion and then you take your proportion, what you're going to

get, and then say whether the 95 percent confidence interval was around your proportion, overlapped that fixed proportion or not.

Now, the other way you can do it is you can assume that that proportion is not fixed, and that has a variation around it. And then you take your rate and that has a variation around it, and how you try to do a sample size. And there are two ways to do a sample size and then of course you'd come to different numbers doing it a different way.

DR. LAINE: I think there are other ways of doing it, too.

DR. SINGH: I'm sorry?

DR. LAINE: I think there are other ways that people have done it too, though.

DR. SINGH: I mean, these are sort of the most two common ways to apply to us both.

CHAIRMAN PETRI: I'm going to ask us to now take a 10-minute break. It's time.

(Whereupon, the foregoing matter went off the record at 3:53 p.m. and went back on the record at 4:03 p.m.)

CHAIRMAN PETRI: Now, because we only have one hour left and we have a lot to cover, I'm going to ask us just to table that issue, the statistical

analysis, because I think the equivalence trial statistics is confusing to many of us.

We have a major toxicity issue that we need to focus on, and that's the renal toxicity. So this is question 3, the discussion of renal, bone, and reproductive toxicity associated with COX-2 and other agents.

This morning I thought we focused quite well on this issue of what sub-populations we thought would need to be studied. Dr. McConnell and Dr. Welton had advised us the sub-populations that were very important to study were: people on Lup diuretics, patients who had creatinines greater than or equal to two milligrams per deciliter, the elderly, and staple hypertensives on different drugs, especially ace inhibitors.

Let me ask Dr. McConnell if there were other issues. Well, we talked a little bit on cirrhosis, congestive heart failure, and Dr. Welton thought that that was sort of a general group of people who were at risk because of the issue of volume depletion. Dr. McConnell, do you want to elaborate on our discussion this morning?

DR. McCONNELL: Well, I think the cirrhotics and the patients who have congestive heart

failure would be reasonable to focus on. Again, my understanding of the literature is those who have reasonable cell presentation, really are not at particular risk. I'm talking about, you know, acute renal failure, the fluid retention, the edema, mild increase in blood pressure. It's probably not important from that standpoint.

And the other group of people I think, included those who were on thiazide, diuretics -- because of their risk for fairly substantial fluid and electrolyte disorders.

CHAIRMAN PETRI: Can you help us with the appropriate length of study? I think for the drug-drug interaction with Lup diuretics, Dr. Welton suggested one month, but for the other at-risk populations, maybe two weeks. Is that appropriate? Can you help us with that.

DR. McCONNELL: Well, I think, at least two -- I'd probably expand that out to a month as well. I think it's probably true that within two weeks you're going to capture most of those people who are going to -- you're going to develop the edema within two weeks.

The small rise in blood pressure that I mentioned, you'll develop that within the first

several weeks. The acute renal failure -- two weeks, maybe a little shorter -- a month is probably more appropriate.

Even then there probably can be some individuals that you're not going to have, just simply because they're not the right substrate at that point, but then will go on to develop that. In other words, they will inadvertently take another agent or become volume contracted and so forth.

And so it would be fair to say within several weeks -- within several days, probably, of the second insult they're going to develop acute renal failure.

I don't think it's sufficient to say that if you put someone on a -- and I'll just say non-steroidal generically -- whether it's COX-1 or COX-2 -- I think it's probably unfair to say that they're going to develop acute renal failure within one to two weeks or a month. Because what drives that are other clinical parameters.

And then finally, the idiosyncratic is tubular interstitial disease with a minimal change from aereolopathy. It's something that's going to develop -- get typically within several weeks or several months.

CHAIRMAN PETRI: But that would be so rare that that would just be the focus of post-marketing, perhaps?

DR. McCONNELL: Yes, exactly.

CHAIRMAN PETRI: Can you help us on this discussion in terms of what the endpoint should be in terms of the renal toxicity besides the obvious of electrolytes, creatinine, GFR? What other things do you want as endpoints?

DR. McCONNELL: I think the -- what you'd really -- one would be a rise in blood pressure. I think edema assessment would be difficult unless you were to say, you know, you'd see small parts. I think the question is really going to relate to a decrease in GFR. In other words a rise in creatinine.

Unfortunately, rises in creatinine are notoriously misleading because should -- GFR declines initially secrete more creatinine, so a rise in creatinine may not be nearly as informative as it ought to be.

But I think if you were to look for, by some criteria, a 20 percent, 25 percent, maybe even a 30 percent rise in creatinine, I think that would be a reasonable endpoint.

CHAIRMAN PETRI: Well, let's open this up

for the entire committee. Other thoughts? Dr. Katona, what about children in terms of renal toxicity?

DR. KATONA: By and large, except for a few special situations, renal toxicity is really not the problem for the children. So I would not take any extra precautions for the children.

CHAIRMAN PETRI: Other thoughts? Let me ask Dr. Witter, or Dr. Hyde, Dr. Weintraub -- any specific issues in terms of the renal toxicity study designs that you wanted to bring up? We're okay?

Dr. Palmer had a comment?

DR. PALMER: Yes, I think it's important that any study that's attempting to show that there's not an effect on renal function has to have a positive control, because if you select a group of patients that are essentially normal, no NSAID is going to cause a creatinine increase.

And if you take somebody that's really severely impaired you'll have problems with almost anything. So you have to have that person that's in the middle that you're going to tip over with a known NSAID that will do it, but not with the drug you're looking at.

CHAIRMAN PETRI: I wonder if that's going

to be a difficult issue in terms of IRBs. Let me ask Dr. McConnell -- a comparator NSAID as we look for renal toxicity.

DR. McCONNELL: I'm not sure I quite understand what you're getting at.

CHAIRMAN PETRI: Well, to address Dr. Palmer's question, is it any good just to show that this new drug does not have renal toxicity in these sub-populations? Do we have to show that another NSAID did?

DR. McCONNELL: I think that probably would be more useful -- I'm not sure that you'd necessarily want deliberately though, to be tipping people --

CHAIRMAN PETRI: That's why I mentioned it. This is an IRB concern, in my view. It very well might be.

DR. McCONNELL: Right. I think it harkens back a bit earlier to Dr. Madrid's point. I mean, I wouldn't -- he raised the point of transient renal failure. It's hardly a benign entity in that these people in the long run are not going to again, have normal kidney function, and that probably as they become older are going to more rapidly deteriorate.

CHAIRMAN PETRI: Dr. Welton, if I could

ask you to address this point first, and then whatever comments you have. So do we have to have a comparator NSAID?

MR. WELTON: No, I would be absolutely opposed to that. I think the population to study are those with stable, pre-existing renal impairment. We know that a priori they are an at-risk group. We know the breakpoint as I mentioned in the morning, is circa two milligrams. Actually, to be precise from the published data, 2.2.

So I would suggest that in looking at this issue one would recruit a population with a serum creatinine in the range of 1.5 to 3. For example, I would use serum creatinine since that's a real world marker of what the clinicians are going to use in practice to make the decision to continuing or discontinuing the drug.

I would then suggest that a level of 0.5 of an increment during therapy would raise a red flag, because that puts you into 95 percent confidence intervals of confidence that that's a real elevation.

If the creatinine doubled from baseline then that should be an automatic stop point of the trial. In such a trial, the patients would also be susceptible to the development of hyper k lemia, so I

put in stop points relevant to elevation of potassium.

But under these circumstances, the gist of it is, I do not think you need an active comparator because if you do put them on something such as indomethacin, then if they're getting an adequate dose they will run into trouble. You know that already so I don't think one really needs it under those circumstances.

CHAIRMAN PETRI: Thank you. And you had a comment as well?

DR. WELTON: The other comment was, as I listened to the development plans, it would suggest that the database is going to be at end, most drugs of anywhere from maybe 3,000 to 10,000/12,000.

And that would provide the opportunity to dredge through the database for all known syndromes and to look for issues of drug-drug interaction, such as Dr. McConnell has already mentioned in relationship with the diuretics.

I would be concerned to look at potassium-sparing diuretics; to look at potassium supplements; ace inhibitors; and additionally then, to look at drug disease interactions or drug-drug disease interactions such as some of these drugs I've just mentioned; individuals with pre-existing diabetes who would be

particularly likely also to develop the problem of hyper k lemia.

CHAIRMAN PETRI: Thank you. Dr. Fernandez-Madrid, then Dr. Simon.

DR. FERNANDEZ-MADRID: I have a question. If anybody knows, flosolide presently a COX-2 inhibitor was rejected for renal adverse effects. Do we know something about this? Why was it?

CHAIRMAN PETRI: Dr. Weintraub.

DR. WEINTRAUB: If we knew anything about it, we couldn't tell you. So we can't really discuss anything about it.

DR. FERNANDEZ-MADRID: All right.

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: Actually, I was going to ask Dr. Welton a question about what he's suggested. In suggesting the use of serum creatinine, a typical, clinically evident measurement that most physicians understand, and given the parameters that you discussed for a poor result from this particular class, would you want to design this trial with several baseline measures to determine the range -- particularly in that particular patient population -- and that why would you not want to use creatinine clearances or some other methodology of clearance, to

be more clear about the real subtle responses?

DR. WELTON: Dr. Simon, I've always thought you were clairvoyant. I agree completely, at the run-in phase one would need to establish that the patient population being studied is indeed, truly a stable population of chronic renal failure and repetitive number of creatinines over a defined period of time.

The creatinine clearance would be a very nice supplement and in fact, I would, under the circumstances of such a trial -- based on what Dr. McConnell pointed out, that creatinine clearance has a tendency in adults, when you drop below a GFR -- glomeric filtration rate -- circa 30 or 35 mils per minute to be a lot less accurate as a true marker of glomera filtration.

Since this would be a relatively limited number of patients in a special population, then I would recommend that as a component part of the trial, DTPA -- technetium DTPA GFR measurements or iothalamate clearances would be added.

But I'd be very careful about adding and making sure the creatinine -- serum creatinine as a major representation. Because that's what our colleagues in the clinical trenches will use.

CHAIRMAN PETRI: Dr. Liang.

DR. LIANG: Could I add to that? I'm concerned just like Lee, that this is -- using creatinine as sort of a stop point is really trial by fire, because we've heard that, you know, when the creatinine bumps you've incurred permanent damage, and that, you know -- in the future as in the present. So I think you would want the most sensitive measure before the creatinine bumps up.

DR. WELTON: No, you don't incur permanent damage, this is purely --

DR. LIANG: I heard that from another of your colleagues.

DR. WELTON: This is a hemodynamically mediated form of renal --

DR. LIANG: Is there data on that point?

DR. WELTON: Pardon? Are there data?

DR. LIANG: You mentioned a point before --

DR. McCONNELL: Yes, I think that if you -- patients who have acute renal failure, even though it's reversed, if you follow those people long-term I think they don't have normal kidney function, I think they're --

DR. LIANG: That's my point.

DR. McCONNELL: Yes, that's my concern, is that --

DR. LIANG: Creatinine is sort of trial by fire. I think you need a more sensitive, functional test to get the most sensitive, early endpoint, because you don't want to subject patients at risk.

DR. McCONNELL: See, my concern is, I think you're always better off with more glomerialyte than fewer gomerialyte. So I think if you have acute renal failure --

DR. LIANG: And I don't really see it as trivial because you know, there's now a lot of data coming forth in the African-American population about fewer gomerialyte - whether that might translate ultimately to higher incidence of hypertension, higher incidences of focal and circumlental glomerulosclerosis.

So that's the only reason I raise that. The issue of the creatinine, whether you wanted to take creatine clearance or average creatinine clearance and urea clearance, which -- the combination of the two would give you a better mark perhaps for GFR -- my only concern is, you know, as we've talked about here, the population we're going to be studying is not going to be a normal population. It's going to

be an older population.

As we age anyways our GFR declines -- just wear and tear, whatever reason. So that a creatinine of 1.2/1.3 is going to be fine in the people in this room. On the other hand if you have a patient with arthritis, he's perhaps 65 years old, more debilitated -- that is a GFR that's probably more in the range of 30 cc's or 40 cc's.

CHAIRMAN PETRI: Dr. Welton, another comment?

DR. WELTON: Yes. In the sub-population that I'm suggesting for study, I was identifying stop points based on serum creatinine. If one stops the patient at a doubling of baseline serum creatinine, the existing data are that it takes about 72 hours for a return to baseline -- to the starting level.

It is a little bit longer with indomethacin, but there's no available data to show that in this very specific tight model, pre-existing chronic renal impairment, that one does something permanently deleterious.

Now, I agree completely with Dr. McConnell on other issues of damage produced to the kidney -- either the nephrotic syndrome or acute capillary necrosis -- which tends to be a high dose phenomenon,

short-term exposure in a very dehydrated individual at the outset of their taking the drug.

That obviously will give a permanent form of damage.

CHAIRMAN PETRI: Thank you. Let me ask Dr. McConnell, are there other issues that he wants to bring up in terms of the renal toxicity studies?

DR. McCONNELL: Not offhand.

CHAIRMAN PETRI: Let me ask Drs. Weintraub, Hyde, and Witter, other issues? We're okay?

There are two other issues that we want to discuss: bone and reproductive toxicity. And I thought maybe we'd want to expand bone to talk about cartilage toxicity as well.

If I could ask Dr. Brandt to begin this discussion?

DR. BRANDT: Cartilage toxicity of NSAIDs. A lot of it, yes, there is much to say. It's not clear that any NSAIDs adversely affect articular cartilage in humans -- in people. The story I guess, begins back around 1970 where clinical observations, I think chiefly by Lou Solomon -- who was an orthopedist in South Africa at the time -- led him to write about analgesic arthropathy -- patients,

particularly taking indomethacin for osteoarthritis of the hip.

He felt accelerated degeneration of the joint was the worst disease than if they had not been treated with indomethacin. There were other anecdotal reports that came to the same conclusion; stress anecdotal reports.

Then some years after that there were a series of studies of the effects of first salicylates, but then a variety of non-steroidals and chondrocyte cultures or organ cultures of articular cartilage from humans or animals that had been used as models of OA.

Which produced results all over the place. There were some NSAIDs that stimulated proteoglycan synthesis or other activities of the chondrocyte and others which were neutral and others which slowed, inhibited synthesis of cartilage matrix macromolecules.

People put a spin on those observations and concluded that the NSAIDs that stimulated synthesis by cartilage cells were good or chondro-protective, and ones that in vitro inhibited metabolism were bad.

There was very little in vivo data for the reason I mentioned this morning. All of the animal

species that are used to study osteoarthritis -- either surgically induced or spontaneously evolving OA -- are exquisitely sensitive to the GI side effects of NSAIDs so that they don't survive long enough to develop OA when they're treated with NSAIDs.

However, there were data in C57 black mice, by Wilhemi and Meyer, that indicated that salicylate feeding in that model, accelerated and increased the severity of osteoarthritis. And there were data from our lab in a canine curciate deficiency level -- surgically induced model of OA -- that showed the same thing, and it didn't matter whether it was aspirin or sodium salicylate.

There were almost no other in vivo data in animal models until recently. Peltier, also using the cruciate deficiency model showed that tenidap protected against the development of osteoarthritis, but that was with co-administration of ometrazone to protect the GI tract.

And that's about the sum and substance of the animal data. There have been two, I think significant studies done -- again with indomethacin in humans -- purporting to show that in patients who already had OA and significant OA, indomethacin administration accelerated the disease, made it worse,

shortened the time to surgery.

One paper by Rashad and also the link study more recently -- a large study from the U.K. by Ted Huskasan in comparing indomethacin, teaprofenic acid, and acetamol -- and purely a radiographic study in the latter case with an x-ray method that Huskasan had devised to measure the rate of drugs basinarily.

Both I think -- just to make a long story short -- both the Rashad study and the Huskasan link study I think, had significant problems with design, with analysis, and interpretation, and there were accompanying editorials of both of those articles that pointed out a number of those limitations and problems.

So I think it's fair to say that at this point there's no persuasive data that any NSAID adversely affects the progression of osteoarthritis accelerates the disease, nor is there any good data -- any data in people -- that it favorably modifies the progression of the disease or prevents the development of the disease.

CHAIRMAN PETRI: Do you have any recommendations in terms of what sort of monitoring should be done for new class of NSAIDs?

DR. BRANDT: The recommendations of OARS

-- the Osteoarthritis Research Society, which has looked at the development of guidelines for studies of OA drugs and made their recommendation -- at least in studies which are long-term, in which therapy is continued for at least a year, to at least get a baseline and follow-up radiograph.

CHAIRMAN PETRI: Knees?

DR. BRANDT: Knees.

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: Only because the drugs we're considering may or may not be non-steroidals, there is data in the literature that's been published by one of the members of our committee, about the effects of these drugs on cartilage, and demonstrated that in fact, in osteoarthritis in vitro.

So they take the piece of cartilage, put it in a petri dish, grow it up in tissue culture so it's an unusual model -- we don't usually see this very much -- not just taking chondrocytes but actually a piece of cartilage -- that COX-2 is actually up-regulated in that circumstance.

Their interpretation was that it was possible that COX-2 was up-regulated as a repair phenomenon, and then they raised the question, could high-grade COX-2 inhibition then lead to cartilaginous

damage?

The alternative explanation could be that COX-2 was up-regulated in the process of actually obtaining the biopsy, and since it was up-regulated in all the pieces that were within the tissue culture dish, that then the circumstances, which then may be an artifact of the experimental model.

But nonetheless, it does raise the question -- and it relates also to bone -- that there may be obscure issues that we have to be concerned about, that yet may not come to clear light until large numbers of patients have been treated with these drugs for a long period of time.

However, with the issue of bone, because of the published data that perhaps there are osteoblast functions related to COX-2; meaning when you take bone slices, put them under gravity or under stress -- sheer stresses or stretching the periosteum -- there seem to be up-regulation in the ex-vivo model of COX-2 activity.

This has been interpreted as perhaps important for the bone to make new bone under weight-bearing conditions. Whether that's actually true or not we have no idea. In our book we have a large series of background documents regarding prostaglandin

bone and all of that has to do with bone loss under conditions of elevation and local prostoglandins; particularly as seen in rheumatoid arthritis associated with juxtarticular osteopenia.

Whether that actually is translatable, it's unlikely that these drugs will cause bone loss under those circumstances. However, all of this leads me to the observation -- I'm very concerned about this in children. And I think that's the key issue as to whether these drugs could then be seen and used in children based on the observations in adults.

And I think that I would be very concerned without clinical trials in children before their epithesis fuse, as to exactly what these effects would be.

I'm less concerned in the adult of bone effects that are substantial, so that I wouldn't require long-term dentatometry studies for things like that. But I'm very concerned about this in children.

CHAIRMAN PETRI: Can we separate out the two concerns in adults, Lee? Would you be interested in a small subgroup with dexadata?

DR. SIMON: No, I would be interested in adults in trying to define -- if we ever could reach consensus and agreement -- what it would mean to do a

structural analysis and outcome in osteoarthritis patients as it relates to the effect of both non-steroidals as well as this new class of drugs.

I'd be very interested in knowing how they actually -- and to answer this question once and for all -- I'm tired of grappling with it; I think we need a good trial to answer that.

From the point of view of bone effects in the adult, I'm not -- I see no evidence -- and I'd like to see the clinical trials to further that evidence -- unless there's evidence of kidney effects related to proteinuria, of phosphorus loss, loss of bicarbonate or other evidence of Vanconi Syndrome, or any other evidence that would suggest there's some metabolic abnormality going on that lead to bone loss -- I don't think that the data suggested now in the pre-clinical sphere and in the in vitro arena, is enough to suggest that there's any clinically significant bone effects to suggest that I'm worried.

CHAIRMAN PETRI: In children -- to bring it to the next set -- in children, do you want x-ray studies?

DR. SIMON: I'm very concerned about this, and you know, I'm really -- this is out of my league. I'm not entirely sure what would be useful trials in

children. I would ask our Pediatric colleagues to answer that question for me.

CHAIRMAN PETRI: I'll ask Dr. Brandt to wait and we'll go to Dr. Katona. What do you want to see in trials in JRA?

DR. KATONA: I would divide the pediatric population into two: one before the epithesis fuses -- and in that population you would worry about bone growth; and then bone mineralization is really, for the majority of your life, happens in adolescence, and that's different issue.

How to address bone growth, that's a difficult one. Probably MRI scans are the best. They are expensive but that's probably the best because that's the way you would see the cartilage and the bone combined with x-ray alone.

So in the pre-pubertal children that would be your best study. And the adolescents, I think that would be just like on the adult deck, so any other bone mineralization parameters.

CHAIRMAN PETRI: Dr. Brandt.

DR. BRANDT: Yes. The problems relative to NSAID effects on articular cartilage may not be accountable for only in the relation of prostaglandin metabolism. Indomethacin, which was a much more

potent prostaglandin synthase inhibitor than salicylate, had no effect on proteoglycane synthesis -- where salicylate knocked it down 30 percent and we had others that were quoted.

That salicylates and Ibuprofen™ and maybe some of the other NSAIDs act not through prostaglandin inhibition but by inhibiting the enzymes that are involved in protoglycane and biosynthesis -- the glucotransates, for example. So it's a complicated business. But none of that translates into any human clinical trial data.

CHAIRMAN PETRI: So this is a difficult issue because we're trying to discuss study designs for toxicity with very little human data, or none.

DR. BRANDT: If I can make one more point to back up to what I said a moment ago, in terms of the OARS Foundation; that at least you get an x-ray, if a patient's been on a drug for OA for a year.

Plain old, conventional, clinical standing x-rays won't do it because the variability from exam to exam in the clinical x-ray is so great they would be worthless. It can be done, if care is taken with regard to standardization of positioning, but not to just sending the patient to the x-ray department.

CHAIRMAN PETRI: Let me ask Dr. Simon

first.

DR. SIMON: Actually, I would talk more about ovarian function --

CHAIRMAN PETRI: Well, okay. Well, I just wanted to make sure before we leave bone and cartilage, that there aren't other issues that Drs. Weintraub, Hyde, and Witter wanted us address.

I think we need a little bit of introduction about reproductive concerns. Perhaps -- I'm sorry. Dr. Johnson.

DR. JOHNSON: Well, one question for Dr. Katona. Is there any animal model that has looked at MRI use as you suggested, for pre-fusing bones?

DR. KATONA: Not that I know of. But there are some clinical studies looking at smaller children, and at the current time it's very clear that in small children that's the only way we can really follow bone development as well as the clinical staging of our trials.

Since children have such a thick layer of cartilage and then they have the growth center that otherwise there is just no way. By the time you see x-ray changes, we've lost the game.

CHAIRMAN PETRI: Dr. Fernandez-Madrid.

DR. FERNANDEZ-MADRID: The other problem

that may be influenced by these news drugs is that periarticular osteoporosis in inflammatory joint disease. And I think this has been shown that it is depending on local factors, on cytokines, either one.

So these possibly could be influenced in a positive way by invading the inflammatory process in the joint. I think this could be counteracted perhaps by the effect on wound healing. There may be more than one effect on these.

So it may not be a bad idea to look at bone mineral density around the joint in some small subset of patients.

CHAIRMAN PETRI: So what we've recommended is in the OA studies, pre- and post-knee x-rays as long as everything is standardized?

DR. BRANDT: At least if they're on the drug for a year.

CHAIRMAN PETRI: And Dr. Fernandez-Madrid is bringing up a quantitative assessment with hand x-rays. Dr. Simon.

DR. SIMON: I think it's an interesting idea. I'm not entire sure it's been validated as a methodology other than commercially; that they've sold people instruments based on the idea that it would be an interesting way to follow patients.

I'm a little concerned about the application of this particular technology as a measurable event, unless we do very standardized x-rays that would then look at juxtarticular osteopenia. I would be very interested in determining if in fact, that there was a biologic effect in that regard, because then that would begin to suggest that truly this is a different class of drugs. Because we do not see that happen with the presently available non-steroidals, and that has been looked at.

But I do want to distinguish that from systemic osteoporosis and doing a total body bone densitometry test, which I'm not entirely sure there's any evidence to warrant its use. It would be interesting to do but I'm not sure it should be required.

CHAIRMAN PETRI: Dr. Brandt.

DR. BRANDT: Yes, there's another aspect to this, and rather than looking at the trabeculae, this discussion raises another interesting issue, I think. In OA it's by no means clear what the origin of joint pain is. Because NSAIDs work we tend to conclude that it's due to synovitis, but that's not necessarily true and there are clearly studies that show that, at least in some patients, the pain

originates in bone.

It's related to altered hemodynamics and stasis of bone, and decreased oxygen tensions, and increased lactate and CO_2. And you can relieve the pain in OA joints by drilling the bone as they might do sometimes in Baltimore for osteonecrosis.

CHAIRMAN PETRI: I don't know how to take that.

DR. BRANDT: But to the point, there was an elegant Scandinavian study a few years ago, in inflammatory arthritis in rats and carrageenan model, showing the same types of abnormalities in bone blood flow that I've just described, as occurring in OA. And all of those abnormalities were relieved with intravenous naproxin.

And I think to suggest that some consideration be given to studies of bone blood flow, that might relate to changes in rheumatoid disease and periarticular osteoporosis on the one hand and to osteoarthritis and the basis for osteoarthritis pain on the other, might be very interesting.

CHAIRMAN PETRI: But you're suggesting this in terms of forwarding the knowledge of basic science. You're not mandating this as important --

DR. BRANDT: That's right. Mechanisms of

symptomatic.

CHAIRMAN PETRI: I'd like to have both Drs. Witter and Simon perhaps, introduce their concerns about reproductive function and what they'd like the committee to address.

DR. WITTER: This concern is, like the other concerns related to bone for example, something where we are trying to extrapolate to some extent, pre-clinical or other information to non-existent clinical data.

You may be familiar with a paper in Cell, I believe it was in October, that described some of the COX-2 knockout mice and some of the reproductive sequelae from that. I just wanted to take this opportunity for the committee to think about in that sense, are there any special concerns that they might have in relationship to these compounds?

CHAIRMAN PETRI: Dr. Simon.

DR. SIMON: It turns out that that observation has been carried a little farther. We now understand, at least in mice, our relatives, that ovulation and implantation of a fertilized egg is dependent upon COX-2 activity.

And furthermore, there have been much to my surprise in doing literature research, actually

several case reports from the U.K., of young women who became infertile when they were put onto Ibuprofen™ in particular -- I'm not beginning to suggest it's unique to that drug in this context -- and that when the drug was stopped they become fertile again. It's a total of five patients.

Anecdotal to say the least; this is not a clinical trial. But it raises the question as to whether or not, in fact, it's common enough but people don't think about it so therefore maybe it's happening. Maybe infertility is not addressed in that way from the point of view of knowing whether they take over-the-counter products or others. All of these people were taking over-the-counter Ibuprofen™ in the U.K.

But raises the issue about what would happen in high-grade, long-term inhibition of COX-2 activity. Perhaps since we don't see it that commonly in the presently available non-steroidal family, all of which inhibit both COX-1 and COX-2, it's not clearly happening as an epidemic, but would it happen differently in people who are exposed for very long periods of time?

And I suspect that the clinical trials may not give us a lot of information about that. So I'm

a little concerned about that.

CHAIRMAN PETRI: Well, they probably aren't going to give us any information because we're not going to be watching women through their cycles. So is it important to have a subset of patients in a clinical research center who are watched over through an entire cycle?

DR. SIMON: I would like to see that.

CHAIRMAN PETRI: Dr. Harris.

DR. HARRIS: I just got acquainted with some of the animal data and I was very concerned about that. And really, I'm even bothered about even trying the clinical trial, unless of course -- because the difficulty there is what do we do?

Half of them are on contraceptives, presumably. Are you looking at fertility? Suppose some of did, in fact, conceive, then there is obviously more, you know, teratogenicity.

DR. SIMON: Or even more.

DR. HARRIS: Yes --

DR. SIMON: Even worse because it's not just teratogenicity; it's that, you know, we know that if you remove COX-2 in mice and if the gene isn't there at birth, you've got serious developmental problems. I'm not sure that we can understand how

this drug can even be used in potentially pregnant people at all.

CHAIRMAN PETRI: So there's concern, but now let's take that concern into how we would design studies to address this -- addressing the issue of its effect on ovulation. That should be accomplishable with, you know, like a 35-day study of a group of women who are cycling.

DR. LIANG: Who would sign up?

CHAIRMAN PETRI: Well, I mean, you pay volunteers for these types of studies.

DR. SIMON: This presumably is not a permanent effect because it has not been observed that way. I prefer this not to be the most expensive contraceptive ever developed, but I do think that we need to understand what's happening there. Well tolerated.

CHAIRMAN PETRI: The other populations we've been talking about, OA and RA, would be predominantly post-menopausal women, though of course we recognize that RA can occur in younger women as well. So I do think it's important that there be a sub-population of women studied throughout their cycle.

This of course, does not get into the

issue of its use during pregnancy. Dr. Johnson. I think Dr. Johnson better come to a microphone.

DR. JOHNSON: Is there any animal data already, vis-a-vis reproductive effects?

DR. SIMON: The COX knockout.

DR. JOHNSON: No, but nothing else that's been rolled the FDA already? I mean, these products have to be screened. I mean, presumably we screen these things to a degree.

CHAIRMAN PETRI: Are there people here who can address the pre-clinical data? Yes? Please introduce yourself.

DR. ISAACSON: Peter Isaacson from Searle. I think there's a wealth of pharmacological data out there about this issue, and one of the things that we need to keep in mind is that what you obtain with a genetic knockout is not the same as what you obtain with a pharmacological agent. It's very hard to achieve 100 percent inhibition of any enzyme -- probably impossible.

The experience that we've had with a couple of agents that are specific COX-2 inhibitors is that they look pretty much like a non-steroidal in terms of their effects on the reproductive system, and that they're not -- there aren't any effects

particularly in fertility at very high doses over long periods of time.

So again, our experience pharmacologically is a little different than what's seen in the genetic experiment and again, based on the pre-clinical data that will be presented to the FDA, we would expect to have a label saying something about the reproductive data that would be just like a regular, non-steroidal.

CHAIRMAN PETRI: Thank you. Another comment from the audience.

DR. SILVERMAN: Dr. Bob Silverman from Merck. I just wanted to confirm that in our experience as well. That the effects seen with COX-2 specific agents appear to be quite comparable to that seen with non-selective agents. There's nothing unique about the COX-2 selective agents, particularly.

So that we would also anticipate that -- we would be held to the same rigor as non-selective agents, and whatever labeling was appropriate for non-selective agents we would assume we would see with regard to the COX-2 specific agents. But there's nothing to suggest any additional issues.

CHAIRMAN PETRI: Well you know, what's happened, especially in rheumatology is, we've become a little bit complacent about NSAID use during the

first trimester. I'm not sure we should have that sense of complacency at this point without the COX-2 selective NSAIDs.

Now, let me ask Dr. Simon for a comment on that.

DR. SIMON: You know, the fetal effects of non-steroidals have been studied significantly in large population studies, and most people have come down to, that they're most comfortable with aspirin and the salicylates, and they're less comfortable as they get to the newer, non-steroidal anti-inflammatory drugs, that are studied less, because they're just used less over time.

The experience is, is that at least by report, that in Rhesus monkeys that the newborn is smaller and has more bruising. In human babies it's very similar. Occasionally there are actually larger feti, and nobody really understands that.

The problem is, is that we are getting complacent, and although the animal data would suggest that -- the pre-clinical animal data that we just heard which you've not seen, been able to evaluate critically -- may be justifiably not worrisome.

But with the anecdotal reports that have now been in the Press about fertility problems, and

with the possibility -- not 100 percent inhibition over long-periods of time but rather, much more inhibition than we've seen before, in the COX-2 arena -- I think that a small clinical trial looking at ovulatory cycle in women, is really not unreasonable given its potential impact in the use of this population.

I am less comfortable with thinking about what kinds of studies would be necessary in the first, second, or third trimester about that. I don't know anything. Does anybody know anything about what relates to closure of the ductus? Which is it, COX-1 or COX-2? Which is it? Or is it both? Because that has significant ramifications from the point of view of using it in late pregnancy at all.

AUDIENCE PARTICIPANT: There is some unpublished data that suggested that COX-1 is predominantly expressed in the ductus, but it's not entirely clear again, if that's the case. Again, from the pre-clinical animal studies in rodents, histologically we don't see closure of the ductus. But that's again, a histological study and it hasn't been confirmed yet in an in vivo kind of experiment.

CHAIRMAN PETRI: Other concerns or comments from the committee about the reproductive

issues?

DR. LIANG: Just a question. Any primate data?

CHAIRMAN PETRI: The question is for the audience. Any primate data in terms of --

DR. LIANG: Fertility --

CHAIRMAN PETRI: -- ovulation, implantation, or pregnancy? And I'm seeing some no's.

DR. LIANG: No data.

CHAIRMAN PETRI: So obviously, there would be concerns in the absence of data. Yes? Please come to a microphone.

DR. MUCHAGEE: My name is Dr. Muchagee. I work for HMD 550. When we evaluate the drug we see the effect of any drug in fertility, teratogenicity, and also the maturation -- post-partum maturation. So this is a standard procedure. And so this drug would run through the same screening and test.

But one of the issues here is, prostoglandins evolved out of the reproductive system, where if you remember those we identified in the '30s, 1930s, with von Euler. So there is definitely a role of prostoglandins in the reproductive system.

But if you see the data of prostaglandin inhibitors in these reproductive screening in animals,

there is a big difference in the effect despite the fact all these drugs are inhibiting prostaglandin synthesis.

So we just don't understand, but we know one thing very sure: that is the effect of ductus closure and also the distortia and things like that. But if we see that COX-2 individuals have some deleterious effect on the ovulation and things like that, that may be related to the prostaglandin as such, but then selectivity of COX-1 or COX-2.

But another thing you have to remember that if COX-2 inhibitors induce any changes in the ovulation and fertility, then we have a real big problem as Dr. Simon suggested; that it is a very expensive contraceptive. Because then the self-effector is different because these drugs maybe go to the use of the normal population. We have to think about that also.

CHAIRMAN PETRI: Thank you. Other comments from the committee? Let me specifically ask our FDA representatives: other issues related to reproduction?

DR. WITTER: Any discussion relating to skin effects, skin toxicity? Is anybody aware of that?

CHAIRMAN PETRI: In my ignorance, can you tell me where there are pre-clinical data that would bring up a concern?

DR. WEINTRAUB: I'm not sure that we have any pre-clinical data; however, there are occasional non-steroidals or drugs that are different, such as phenoxyprofin which caused skin problems.

CHAIRMAN PETRI: I thought you were going to bring up naproxen and porphyria in children. Dr. Fernandez-Madrid.

DR. FERNANDEZ-MADRID: While not related to this scheme it seems -- it is not a particular question here. I wonder if there is data about the brain? Psychologic testing, cognitive tests, memory testing? COX-1 and COX-2 have been localized in the brain, and from our experience with primarily COX-1 inhibitors in the medicine produces a substantial number of problems in this area -- in children also -- and particularly in the elderly.

Piroxicam is known to produce confusion and a variety of psychologic disturbances, so I wonder if there's any data on COX-2 inhibitors?

CHAIRMAN PETRI: Dr. Simon wanted to comment.

DR. SIMON: In particular as it relates to

what we know about the cognitive effects of non-steroidals presently available, there are actually very confusing reports. There are reports that in fact, Alzheimer's disease, progression is decreased in people who are on long-term, low dose aspirin for cardiovascular effects, while at the same time there are confusing reports using -- usually large populations being studied for other reasons.

And then subset analyses of those populations looking at various cognitive testing, demonstrating that some of these patients do worse on non-steroidals, some of those patients do better on non-steroidals; while at the same time we have the confusing anecdotal observations of drugs like indomethacin which induced depersonalization reactions and all kinds of other things, not even including the meningitis induced by some traditional -- particularly phenylproprionic acid derivatives, either over-the-counter or otherwise -- in patients with Lupus, and perhaps even a few other people as well.

I think that the fear is there. We know that from an experimental model point of view in animals that post-seizure, COX-2 is very up-regulated in the brain. It's there and evident, but for the post-seizure syndrome experimentally, it's quite

clear.

What that means, I don't think anybody knows. We also know that in Alzheimer's disease there's not a lot of inflammation that's in the brain, so therefore is COX-2 being up-regulated because of something we don't understand?

It would be nice to have studies like this. Would I require them? I would like to see them. I'm very interested in pushing back the frontiers of science. But from a regulatory point of view I'm not entirely sure it's fair to require it.

CHAIRMAN PETRI: Other than of course, we want all the serious, adverse events combed to see if there is some unusual toxicity. Other comments? Let me ask Dr. Weintraub if he could summarize today.

DR. WEINTRAUB: Yes, well, I'm going to start with 8 o'clock this morning and then -- no. You know, this has been very valuable to us. I think it's been very valuable for everybody. This has given us a fair amount to think about and I really do very much appreciate all of you donating your time and backgrounds and education, etc., to this problem.

But you can see how important and interesting it is. We are faced with this issue all the time of acting on the basis of a little bit of

knowledge. And unfortunately you know, we're right at the edge, along with the manufacturers of many new drugs. We're right at the edge and we're trying to understand it so we can push ahead.

We can't wait around and ask for more, more, more. We have to make a decision now and get it off. And I think this committee meeting was very helpful for us. Thanks.

CHAIRMAN PETRI: Well, I want to thank Kathleen Reedy and the committee. We're now adjourned.

(Whereupon, the hearing was adjourned at 4:56 p.m.)